Remarks

Claims 1-4, 7-22, 24-28, 30, 33-35, 38, and 57-62 were pending in the application. Claims 1-4, 7-21, 30, 33-35, 38, and 57-62 stand rejected, and claims 22 and 24-28 have been objected to as depending from a rejected claim. Claims 1, 18, 22, 24-28, 57-59, and 61 are amended as above. Claims 4 and 60 are canceled by the present Amendment. Claims 63-74 have been added. Support for claim 63 and 65, which recite cyclopropyl radicicol in a pharmaceutical composition and in the treatment of cancer, is found in Figures 17-21. Support for claim 64 and 66 reciting the use of cyclopropyl monocillin (also known as deschloro-cyclopropyl radicicol) in a pharmaceutical composition or in the treatment of cancer is found in Figures 17, 18, and 21. Support for claim 67, 71, and 72 is found on page 21, line 1 through page 22, line 6. Support for dependent claim 68 is found on page 22, lines 8-13, and support for dependent claims 69-70 is found on page 19, line 15. Support for claim 73 and 74 is found on page 31, line 10, through page 32, line 7. Applicant submits that these amendments including the newly added claims find adequate support in the specification as originally filed and that no new matter has been added by these amendments or additions. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. §112, first paragraph, for lack of enablement.** Claims 30, 33-35, 38, and 59-62 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The Examiner has stated that given the diversity of diseases within the category "cancer" it is "contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases." Even if the Examiner is correct, the claims are enabled because there is not duty to enable every species within a claimed genus. Support for a representative number is sufficient to demonstrate that the full scope of the claimed invention is enabled.

In the present application, data has been included for radicicol, monocillin, and several analogues thereof including cyclopropyl radicicol and cyclopropyl monocillin. These

compounds have been tested against several human cancer lines, including MCF7, BT474, and N417, to show their efficacy at inhibiting the growth of these cells. Therefore, at least four structurally related compounds have been tested in three cell lines to establish their efficacy in inhibiting the growth of cancer cells. Applicant submits that enabling support for a representative number of compounds within the claimed genus of structurally related compounds is sufficient to teach one of ordinary skill in this art how to make and use the claimed pharmaceutical compositions and methods of treatment.

In addition, with respect to the cancers treated using the claimed invention the claims recite "Hsp90-dependent cancers" (claims 30, 33-35, 38, and 62) and "Rb^- cancer cells" (claims 59-61). The compounds of the invention are known to be inhibitors of Hsp90 and thus would be useful in treating Hsp90-dependent cancers. It has also been shown that growth inhibition by radicicol is a result of an Rb-dependent arrest in G1 of the cell cycle. This is supported by reports in the literature from the Danishefsky group as well as others. References detailing the efficacy of radicicol, monocillin, and analogues thereof in the treatment of Hsp90-dependent cancers include: Yamamoto *et al.*, *Angew. Chem. Int. Ed.* 42(11):1280, 2003; Buchner, *TIBS* 24:136, 1999; Chiosis *et al.*, *Chem. & Biol.* 8:289, 2001; Roe *et al.*, *J. Med. Chem.* 42:260, 1999. A copy of these references was provided to the Examiner in the Information Disclosure Statement (IDS) filed November 8, 2001 or is provided with the IDS submitted herewith.

Since the present application was filed, a subsequent provisional U.S. patent application, which includes additional biological data for radicicol analogues, has been filed. This application was filed on December 19, 2003 and was given U.S.S.N. 60/531,092. A copy of the application as filed has been included herewith. The additional data presented in Figures 22-26 provide additional evidence that the inventive compounds are useful in the treatment of cancer as initially described in the present application. Included in these data are the treatment of nude mice bearing a human mammary carcinoma MX-1 xenograft with cyclopropa radicicol (the compound shown in dependent claim 65). Applicant submits that in view of the data presented in the present application, the suggestion in the literature that Hsp90 is a target of radicicol and monocillin, and the further evidence presented in the recently filed provisional application, which includes *in vivo* studies, show that the claimed invention is enabled. The Examiner is

invited to contact the applicant if these data presented in Declaration form would be useful in furthering prosecution.

II. Rejection under 35 U.S.C. § 102(b), as being anticipated by Sugimura *et al.* Claims 1, 4, 13, 18, 21, 30, 33-35, 38, and 59-62 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sugimura *et al.*, U.S. Patents 5,650,430 and 5,597,846. Examiner states that proviso (1) in claim 1 does not exclude all the compounds taught by Sugimura *et al.* In particular, the Examiner points to compounds wherein R_B and R_D are arylalkyl and heteroaryl. Proviso (1) of claim 1 has been amended as suggested by the Examiner. Applicant submits that all of the compounds taught by Sugimura *et al.* are excluded from the claimed invention and requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 102(b), as being anticipated by Lampilas *et al.* Claims 1, 4, 7, 13, 18, 21, and 30 have been rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Lampilas *et al.* (*Tetrahedron Letters* 33(6):777-80 (1992)). The Examiner maintains that claim 1 does not proviso out compound wherein R_1 is hydrogen and points to compound 12 in Lampilas *et al.* as an example of a compound not carved out. Proviso (1) of claim 1 has been amended to include *tert*-butyldimethylsilyl in the definition of R_B and R_D, thereby excluding compounds 12, 16, and 17 of Lampilas *et al.*

IV. Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner has rejected claims 57 and 58 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description guideline. The Examiner maintains that the subgenus recited in claim 57 and the species recited in 58 are new matter and requests that the claims be canceled. Applicant submits that there is written description support for these claims in the originally filed specification.

With respect to claim 57, support for the subgenus can be found by combining the subgenus disclosed on page 21, line 1-page 22, line 13 with the definition of K and L as found on page 19, line 113. One of skill in the art reading the specification would understand that the

subclasses listed starting on page 18, line 6, and continuing onto page 19 could be used to further describe any subgenus of compounds found in the specification. Therefore, the definition of K and L as forming an oxime is combined with the cyclopropyl subgenus on page 21 to yield support for claim 57.

Support for claim 58 can be found in Figure 14, compound **40**. The compound recited in claim 58 is also shown in Figure 17 and 18 (see compound labeled as cyclopropyl radicicol).

Applicant requests that the rejection for lack of written description be removed in light of the support for claims 57 and 58 in the originally filed specification.

V. **Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.** Claims 1-4, 7-22, 24-28, 30, 33-35, 38, and 57-62 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-4, 7-21, 30, 33-35, 38, and 59-62 have been rejected by the Examiner for being vague and indefinite because of proviso (3) of claim 1. The proviso is not duplicated in lines 8-10 as the Examiner has suggested but rather the R groups, Z, and X in those lines refer to the substituents on the second compound of formula (I). This proviso is intended to carve out particular dimers of radicicol. Applicant has amended the proviso to make this more clear by adding the phrase "of the second compound of formula (I)" after each of the R groups, X, and Z in the second half of the proviso. Applicant submits that the amended claim is clear and definite and requests that the rejection be removed.

b) Claim 1 has been amended to recite "OR_B" and "R_B" in the definition of R_2. Applicant thanks the Examiner for pointing out this error.

c) Claim 1 has been amended to recite "OR_D" and "R_D" in the definition of R_4. Applicant thanks the Examiner for pointing out this error.

d) Claim 1 has been amended to make the definition of R_L in proviso (3) definite by reciting "a substituted acyl moiety." The word "acyl" was inadvertently crossed out in the last amendment.

e) Claim 4 has been canceled rendering the rejection of claim 4 moot.

f) Claims 30, 33-35, 38, and 59-62 have been rejected by the Examiner for being indefinite and vague. The Examiner maintains that the claims provide for the use of the claimed compounds but that the claims do "not set forth any steps involved in determining which are the diseases capable of being mediated by inhibiting the growth of or killing Hsp90-dependent cancer cells." Applicant disagrees. The claims as written would be clear and definite to one of skill in the art reading the claims in light of the application.

The claims clearly define the scope of the compounds useful in the claimed pharmaceutical composition and methods. And the claims clearly define the cancers that are to be treated by the claimed method, that is Hsp90-dependent cancers and Rb^- cancers. One of skill in the are could determine whether a cancer is Hsp90-dependent or Rb- using techniques known in the art. Therefore, applicant respectfully submits that the claims are clear and definite and requests that the rejection be removed.

g) Claim 57 has been amended to include the definition of R_L from claim 1. Amended claim 57 is definite and clear.

h) Claim 59 has been amended to end with a period.

i) Claim 60 has been canceled rendering its rejection moot.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Date: August 3, 2004

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A Concise Route to Benzofused Macrolactones via Ynolides: Cyclopropradicicol

Zhi-Qiang Yang† and Samuel J. Danishefsky*,†,‡

Laboratory for Bioorganic Chemistry, Sloan Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and Department of Chemistry, Columbia University, Havemayer Hall, 3000 Broadway, New York, New York 10027

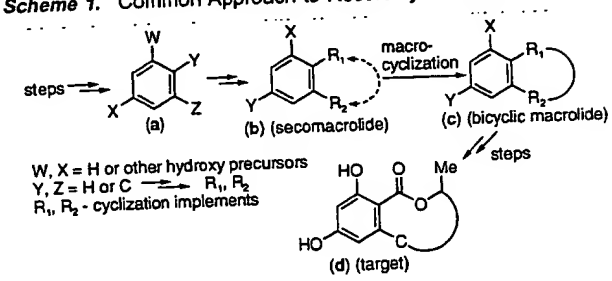
Nature produces a variety of biologically active products (presumably of polyketide genesis), which are comprised of a resorcinylic moiety fused to a macrolactone (cf., **d**).[1] Two early examples of such systems are zearelenone[2] and lasodiplodin.[3] The general approaches to building such compounds in a chemical laboratory have followed, broadly, the sequence format shown in Scheme 1: (i) assembly of an aromatic core, with an actual or virtual resorcinylic functionality bearing minimal benzyl-like handles (cf., **a**); (ii) chain extension of these minimal implements to reach a macrocyclization candidate structure (see **b**); (iii) macrocyclization, followed by (iv) late stage deprotection and other functional group adjustments (see **1**) to reach the target.[1]

Recently, a 14-membered resorcinylic macrolide, radicicol[4] (**1**, Scheme 2), attracted our attention due to its novel antitumor properties. Originally isolated form *M. bonorden*,[4] radicicol shows a high affinity binding to (K_d = 20 nM) and inhibition of the Hsp90 molecular chaperone.[5] Our interest in radicicol arose from a larger program directed to Hsp90 as a potential target in cancer chemotherapy.[6] Other inhibitors of the action of Hsp90 on key cancer related client proteins are based on geldanamycin (**3**) scaffolds.[7] Radicicol, which is also a nanomolar inhibitor of Hsp90, avoids the potential liabilities of the quinone moiety of the geldanamycins. Not surprisingly, in view of our experiences in the epothilone area,[8] we were concerned that the epoxide linkage of **1** might serve as a locus of nondiscriminating cell toxicity. As recently described, we "edited out" the oxido function of **1** through total chemical synthesis, replacing it with a cyclopropane group (see cyclopropradicicol **2**, Figure 1).[9] Following early assessments, **2** is a candidate for drug development, or minimally, a promising lead structure warranting optimization.[9] However, for these goals to be pursuable, it would be necessary to devise a far more efficient and concise total synthesis of precursors to **2** and **2** itself, than had hitherto been accomplished. The chances for achieving major progress through fine-tuning and optimization of our previous synthesis seemed none too promising.

Below, we report a new approach to the broad family of resorcinylic fused macrolides. The underlying concept is captured graphically in Scheme 2, which is directed to our focusing target, cyclopropradicicol (**2**). However, as is suggested by the very facile synthesis of model compound **13** (vide infra), and has been further established in ongoing work,[10] the method is quite general. The central element of our plan is the building of an "ynolide" intermediate and its advancement to the benzomacrolide by a Diels–Alder cycloaddition. The ynolide is constructed through olefin metathesis, enabled only by presentation of the acetylene linakge as its dicobalt hexacarbonyl cluster (see **9** → **10** and **14** → **15**).[11]

† Sloan Kettering Institute for Cancer Research.
‡ Columbia University.

Scheme 1. Common Approach to Resorcinylic Macrolides



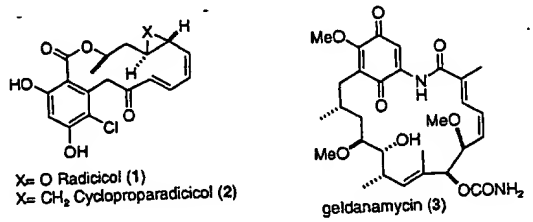
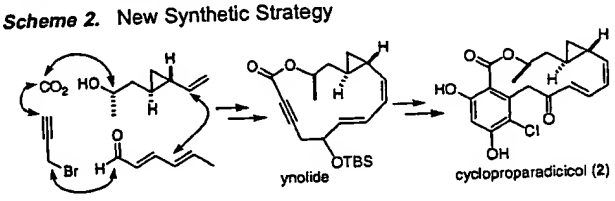
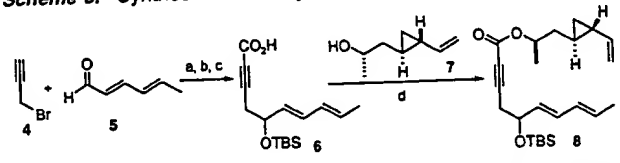


Figure 1. Structures of Hsp90 inhibitors.

Scheme 2. New Synthetic Strategy



Scheme 3. Synthesis of the Acyclic Alkynoic Ester[a]

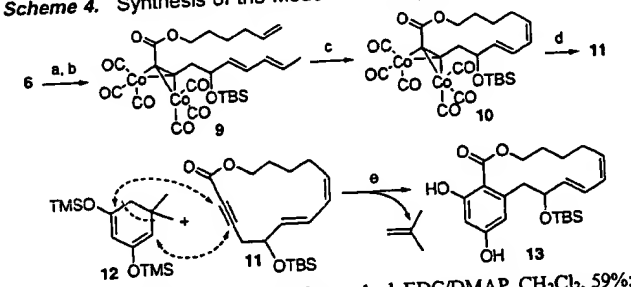


[a] Reagents and conditions: (a) (i) Zn, THF, 66%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 100%; (c) BuLi, −78 °C; then CO_2; (d) DIAD, Ph_3P, THF, −20 °C, 47% (two steps).

Our synthesis commenced with commercial 2,4-hexadienal (sorbaldehyde, **5**, Scheme 3). Reformatsky-like condensation of propargyl bromide (**4**) with **5**, followed by TBS ether protection and subsequent reaction of the lithium alkynide ion with CO_2, provided acid **6**. Following reaction of racemic **6** and the known optically pure and defined alcohol **7**[9] under Mitsonobu conditions, ester **8** was obtained.

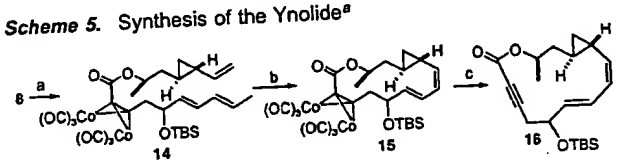
Projected ring-closing metathesis (RCM) reactions were conducted with a cyclic alkyne. Unfortunately, triene **8** failed to cyclize under a variety of RCM conditions. We took this negative finding to reflect impediments to cyclization arising from the linear

Scheme 4. Synthesis of the Model Resorcinylic Macrolactone[a]



[a] Reagents and conditions: (a) 5-hexen-1-ol, EDC/DMAP, CH_2Cl_2, 59%; (b) $Co_2(CO)_8$, PhMe, 86%; (c) second generation Grubbs catalyst (25 mol %), CH_2Cl_2 (0.2 mM), 45 °C, 71%; (d) CAN, acetone, −10 °C, 92%; (e) 140 °C, neat; then SiO_2, 60%.

Scheme 5. Synthesis of the Ynolide[a]



[a] Reagents and conditions: (a) $Co_2(CO)_8$, PhMe, 100%; (b) second generation Grubbs catalyst (25 mol %), CH_2Cl_2 (0.2 mM), 45 °C, 57%; (c) I_2, THF, 0 °C, 69%.

character of the acetylene, possibly aggravated by rigidities associated with the trans-disubstituted cyclopropane. A more flexible model compound was prepared from acid **6** and 5-hexen-1-ol and was subjected to RCM reactions (Scheme 4). Again, only starting material was recovered. Aside from the constraint to cyclization imposed by linear alkyne, the cyclization could further be complicated by nonproductive coordination of the acetylene to the RCM catalytic machinery. It is well known that reaction of dicobalt carbonyl with acetylenes can lead to stable complexes,[12] wherein the geometry of cobalt-complexed alkynes is distorted to approximately 140°.[13]

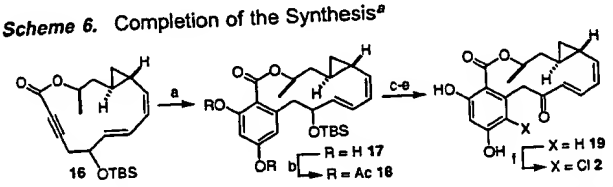
In the event, cyclization of **9** proceeded smoothly under the conditions shown. Following oxidative removal of the cobalt using ammonium cerium(IV) nitrate (CAN), the desired cyclic alkynoic ester **11** was generated in high yield (Scheme 4).

Construction of the resorcinylic skeleton called for a Diels–Alder reaction of **11** with a 1,3-bis-oxygenated diene. We found that the known dimedone-derived diene, 5,5-dimethyl-1,3-bis-trimethylsilyloxycyclohexa-1,3-diene[14] (**12**, Scheme 4), served our purpose best. Indeed, Diels–Alder reaction of cyclic alkyne **11** with **12** proceeded smoothly at 140 °C, providing the desired aromatic product **13** in 60% yield, after concomitant retro-Diels–Alder loss of isobutene from the initial adduct and hydrolysis of the trimethylsilyl ether groups during chromatography.

We applied this strategy to the targeted system (**8**). Gratifyingly, under the same RCM conditions, cyclopropane-containing cobalt complex **14** cyclized to give **15** in 57% yield, as a 2:1 mixture of two diastereomers (Scheme 5).[15] In this case, removal of cobalt on **15**, however, proved to be challenging, presumably due to the presence of the sensitive vinyl cyclopropane functionality. After screening a variety of conditions, we found that I_2–THF worked best.[16] The key cyclic alkyne dienophile **16** was thus obtained in 69% yield.

Diels–Alder reaction of **16** with diene **12** furnished the desired product **17** in 75% yield (Scheme 6). Transformation of **17** to the desired ketone by direct oxidation turned out to be a nontrivial

Scheme 6. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) **12**, 140 °C, neat, 75%; (b) Ac_2O, DMAP, DMF, 87%; (c) HF/Pyr. THF; (d) Dess–Martin periodinane, CH_2Cl_2, 68% (two steps); (e) 5% $NaHCO_3$/MeOH, 92%; (f) SO_2Cl_2, CH_2Cl_2, 0 °C, 61%.

matter. In the end, it was accomplished following protection of the two phenolic functions, as shown, by straightforward transformations to afford dechlorinated analogue **19** (Scheme 6). Finally, regioselective chlorination of **19** using SO_2Cl_2 in CH_2Cl_2[9,17] converted **19** into cycloproparadicicol (**2**).

In summary, a new efficient synthetic route has been developed for a preclinical candidate, cycloproparadicicol (**2**), and, by extension,[10] to a broad range of benzofused macrolactones.

Acknowledgment. Support for this research was provided by the National Institute of Health (CA28824). Dr. Geoge Sukenic and Anna Dudkina are acknowledged for NMR and mass spectrometric analysis. We thank Drs. Kana Yamamoto and William Berkowitz for helpful discussions.

Supporting Information Available: Experimental procedure and physical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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A Concise Route to Benzofused Macrolactones via Ynolides: Cyclopropparadicicol

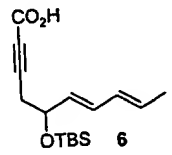
Zhi-Qiang Yang[†] and Samuel J. Danishefsky*[,†,‡]

[†]*Laboratory for Bioorganic Chemistry, Sloan Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and* [‡]*Department of Chemistry, Columbia University, Havemayer Hall, 3000 Broadway, New York, New York 10027*

Supporting Information Available: Experimental procedure and physical data for all new compounds (PDF). This material is available free of charge via the internet at http://pubs.acs.org.

Supplementary Material

General Methods: Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. THF, toluene, and methylene chloride was obtained from a dry solvent system (passed through a prepacked column of alumina) and used without further drying. All air and water sensitive reactions were performed in oven or flame-dried glassware. NMR (^{1}H and ^{13}C) spectra were recorded on Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz as noted individually, referenced to $CDCl_3$ (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C). Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter. Low resolution mass spectra (ESI) were determined with a PESciex AP 130 spectrometer. High resolution mass spectra (FAB) were determined at Chemistry Department of Columbia University. Flash chromatography was performed with silica gel (230-400 mesh) from EM Science as the stationary phase. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds which were not UV active were visualized by dipping the plates in phosphomolybdic acid solution and heating. Preparative thin layer chromatography was performed using the indicated solvent on Whatman® (LK6F Silica gel 60 Å 250 μM or Pk6F Silica Gel 60 Å 1000 μM) TLC plate.



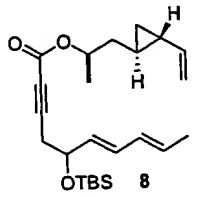
6

Acid **6**. To a suspension of activated zinc (15 g, 230 mmol) in dry THF (50 mL) at 0 °C was added propargyl bromide **4** (19.2 mL 80 wt% in toluene, 172 mmol). The resulting mixture was stirred at 0 °C for 1 hr, and sorbaldehyde **5** (12.7 mL, 115 mmol) was added. After 1 hr at 0 °C, additional zinc (4.5 g, 69 mmol) was added, and stirring was continued for 2.5 hrs at room temperature (the reaction was exothermic and ice bath was needed occasionally to keep the temperature down). The reaction was

quenched by slow addition of sat. aqueous NH_4Cl (500 mL), followed by diluting with Et_2O (1 L). The layers were separated, and the organic layer was washed with H_2O (300 mL), brine (300 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was dissolved in CH_2Cl_2 (750 mL) with imidazole (9.8 g, 144 mmol), *t*-butyldimethylsilyl chloride (19 g, 126 mmol) and 4-(dimethylamino) pyridine (1.4 g, 11.5 mmol), and stirred at room temperature for 3 hrs. Additional imidazole (4.9 g, 72 mmol) and *t*-butyldimethylsilyl chloride (9.5 g, 63 mmol) were added, and stirring was continued for 9 hrs. The reaction was quenched by addition of sat. aqueous NH_4Cl (200 mL). The layers were separated, and the organic layer was washed with H_2O (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 0 to 10% Et_2O in hexane) to give the terminal alkyne precursor of **6** (15 g, 52%).^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.03 (ddd, *J* = 15.0, 10.6, 1.3 Hz, 1H), 5.72 (dd, *J* = 14.9, 6.9 Hz, 1H), 5.61 (dd, *J* = 15.1, 6.4 Hz, 1H), 4.30 (q, *J* = 6.3 Hz, 1H), 2.43 (ddd, J = 16.5, 6.2, 2.7 Hz, 1H), 2.34 (ddd, J = 16.5, 6.8, 1.7 Hz, 1H), 2.60 (t, *J* = 2.6 Hz, 1H), 1.77 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 132.5, 131.1, 130.7, 130.0, 81.7, 72.1, 70.1, 28.9, 26.1, 18.4, -2.7; IR (film) ν_{max} 3313, 2956, 2930, 2856, 2121, 1255, 1115, 1079, 987, 837; ESIMS *m/z* 273 ([M + Na^+], $C_{15}H_{26}NaOSi$ requires 273).

To a solution of the terminal alkyne precursor of **6** (15.0 g, 59.9 mmol) in Et_2O (270 mL) at -78 °C, was added a solution of BuLi (1.6 M in hexane, 41.5 mL, 66.4 mmol). After 45 min, excess crushed dry ice was added and the reaction was allowed to warm to room temperature. The solution was acidified by addition of 0.5 M aqueous citric acid (300 mL). The layers were separated, and the aqueous layer was extracted with additional Et_2O (300 mL x 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 50% to 100% EtOAc in hexane) to give the product as a light yellow solid (17.5 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.03 (ddd, *J* = 14.9, 10.6, 1.3 Hz, 1H), 5.75 (dd, *J* = 15.0, 6.8 Hz, 1H), 5.55 (dd, *J* = 15.1, 6.4 Hz, 1H), 4.36 (q, *J* = 6.3 Hz, 1H), 2.61-2.48 (m, 2H), 1.77 (d, *J* = 6.8 Hz,

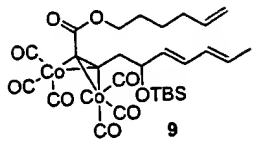
3H), 0.91 (s, 9H), 0.10, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 157.6, 131.6, 131.3, 130.7, 89.7, 74.0, 71.4, 29.3, 26.0, 18.4, 18.3, -4.3, -4.7; IR (film) ν_{max} 2956, 2930, 2857, 2242, 1689, 1281, 1257, 1080; ESIMS *m/z* 317 ([M + Na^+], $C_{16}H_{26}NaO_3Si$ requires 317).



8

Alkynoic ester **8**. To a solution of DIAD (14.7 mL, 72.9 mmol) in dry THF (350 mL) was added Ph_3P (15.8 g, 60.2 mmol), and the mixture was stirred at room temperature for one hour. At -20 °C, a solution of acid **6** (13.1 g, 44.4 mmol) in 100 mL THF was added. After 15 min, a solution of alcohol **7** (4.0 g, 31.7 mmol) in 150 mL THF was added, and stirring was continued for 2 hours at -20 °C. The reaction was quenched by addition of 250 mL of pH 7.2 phosphate buffer, followed by warming to room temperature and diluting with EtOAc (1.5 L). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with brine (250 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 50:1→20:1 hexanes/EtOAc) to give ester **8** as a mixture of two inseparable diastereoisomers (5.9 g, 47%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.03 (ddd, *J* = 12.3, 10.6, 1.4 Hz, 1H), 5.70 (dd, *J* = 14.8, 6.8 Hz, 1H), 5.55 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.37 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 5.03 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.84 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.34 (q, *J* = 6.4 Hz, 1H), 2.56-2.42 (m, 2H), 1.76 (d, *J* = 6.8 Hz, 3H), 1.57-1.53 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.20-1.10 (m, 1H), 0.90 (s, 9H), 0.79-0.68 (m, 1H), 0.65-0.57 (m, 2H), 0.10, 0.05 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 154.5, 141.4, 131.8, 131.1, 130.8, 130.4, 112.1, 86.2, 74.9, 73.0, 71.5, 39.7, 29.2, 26.0, 22.4, 19.8, 18.4, 18.3, 17.2, 13.7, -4.3, -4.7; IR (film) ν_{max} 2955, 2930, 2856, 2238, 1710,

1253, 1068; ESIMS *m/z* 437 ([M + Cl^-], $C_{24}H_{38}ClO_3Si$ requires 437); HRMS (FAB^+) *m/z* 403.2687 ([M + $H]^+$, $C_{24}H_{39}O_3Si$ requires 403.2668).

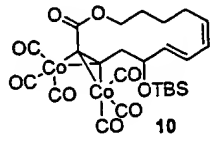


9

Cobalt complex **9**. To a solution of acid **6** (192 mg, 0.653 mmol) and 5-hexen-1-ol (0.118 mL, 0.979 mmol) in dry CH_2Cl_2 (3 mL) was added EDCI (150 mg, 0.784 mmol) and 4-(dimethylamino)pyridine (8.0 mg, 0.065 mmol). After 3 hrs at room temperature, the reaction mixture was loaded on PTLC plates and purified (12:1 hexane/EtOAc) to give the model ester (146 mg, 59%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.18 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.04 (ddd, *J* = 15.0, 10.5, 1.5 Hz, 1H), 5.79 (ddt, *J* = 17.1, 10.3, 7.2 Hz, 1H), 5.71 (dq, *J* = 15.0, 6.8 Hz, 1H), 5.56 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.97 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.35 (q, *J* = 6.3 Hz, 1H), 4.16 (t, *J* = 6.6 Hz, 2H), 2.57-2.44 (m, 2H), 2.09 (q, *J* = 7.2 Hz, 1H), 1.77 (d, *J* = 6.9 Hz, 3H), 1.74-1.63 (m, 2H), 1.52-1.44 (m, 2H), 0.90 (s, 9H), 0.10, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 154.0, 138.4, 131.8, 131.1, 130.8, 130.5, 115.1, 86.6, 74.6, 71.5, 65.9, 33.4, 29.3, 28.1, 26.0, 25.3, 18.4, 18.3, -4.3, -4.7; IR (film) ν_{max} 2955, 2930, 2856, 2238, 1713, 1249, 1072; ESIMS *m/z* 399 ([M + Na^+], $C_{22}H_{36}NaO_3Si$ requires 399). HRMS (FAB^+) *m/z* 375.2363 ([M - $H]^+$, $C_{22}H_{35}O_3Si$ requires 375.2355).

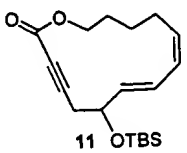
To a solution of the above alkynoic ester (77.8 mg, 0.207 mmol) in toluene (9 mL) was added $Co_2(CO)_8$ (99.0 mg, 0.289 mmol). The mixture was stirred at room temperature for 45 min, and then concentrated in vacuum. The dark residue was purified by PTLC (15:1 hexane/EtOAc) to give cobalt complex **9** (117.5 mg, 86%) as a red oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, *J* = 15.3, 10.6 Hz, 1H), 6.03 (ddd, *J* = 15.3, 11.3 Hz, 1H), 5.68 (dd, *J* = 14.9, 6.9 Hz, 1H), 5.61 (dd, *J* = 15.2, 6.8 Hz, 1H), 5.38 (ddd, *J* = 17.1, 10.1, 8.7 Hz, 1H), 5.10 (q, *J* = 6.4 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.85 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.41, (m, 1H), 3.20-3.15 (m, 2H), 1.76 (d, *J* = 6.7 Hz, 3H), 1.59 (t, *J* = 6.6 Hz, 2H), 1.32 (d, *J* =

6.2 Hz, 3H), 1. 22-1.17 (m, 1H), 0.90 (s, 9H), 0.82-0.72 (m, 1H), 0.66-0.59 (m, 2H), 0.09, 0.08 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 198.7, 169.2, 141.4, 134.3, 132.5, 132.4, 132.2, 131.0, 130.2, 128.8, 127.2, 127.1, 112.0, 93.0, 81.0, 73.7, 73.6, 73.1, 40.0, 26.1, 22.4, 19.9, 18.6, 18.4, 17.4, 13.9, 13.5, -4.2, -4.3, -4.6; IR (film) ν_{max} 2956, 2930, 2858, 2097, 2058, 2029, 1703, 1221, 1065; ESIMS *m/z* 685 ([M + Na^+], $C_{28}H_{36}Co_2NaO_9Si$ requires 685).



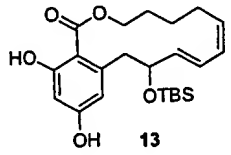
10

RCM product **10**. To a solution of cobalt complex **9** (16 mg, 0.024 mmol) in dry CH_2Cl_2 (120 mL) was added tricyclohexyl phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]-[bezylidene] ruthenium(IV) dichloride (second generation Grubbs catalyst) (6.1 mg, 0.0072 mmol). The resulting solution was heated to 45 °C for 1 hr and 10 min, then cooled to room temperature and filtered through a plug of silica gel. The solvent was removed under reduced pressure. The residue was purified by PTLC (15:1 hexane/EtOAc) to give cyclic product **10** (10.5 mg, 71%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.44 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.97 (t, *J* = 10.8 Hz, 1H), 5.58 (dd, *J* = 15.4, 7.5 Hz, 1H), 5.54 (dt, *J* = 10.1, 4.5 Hz, 1H), 4.57-4.47 (m, 2H), 4.25-4.20 (m, 1H), 3.45-3.36 (m, 2H), 2.45-2.37 (m, 1H), 2.13-1.05 (m, 1H), 1.99-1.79 (m, 1H), 1.80-1.62 (m, 2H), 1.51-1.41 (m, 1H), 0.92 (s, 9H), 0.11, 0.08 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 199.9, 170.4, 135.2, 132.7, 129.0, 127.1, 92.8, 77.4, 73.1, 65.0, 45.2, 26.4, 26.1, 25.4, 18.5, 1.2, -4.2, -4.6; IR (film) ν_{max} 2955, 2930, 2857, 2098, 2059, 2027, 1702, 1213, 1057; ESIMS *m/z* 643 ([M + Na^+], $C_{25}H_{30}Co_2NaO_9Si$ requires 643).



11

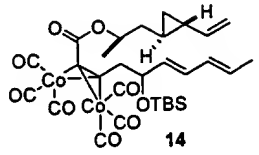
Model cyclic alkyne **11**. To a solution of compound **10** (35.6 mg, 0.0574 mmol) in acetone at -10 °C was added ammonium cerium (IV) nitrate (189 mg, 0.344 mmol) portionwise. After 10 min at -10 °C, the reaction was quenched by addition of diisopropylethylamine (0.18 mL, 1.03 mmol). The resulting mixture was filtered through a plug of neutral alumina, and the solvent was removed under reduced pressure. Purification by PTLC (15:1 hexane/EtOAc) afforded cyclic alkyne **11** (17.6 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.64 (dd, J = 15.5, 11.1 Hz, 1H), 6.07 (t, J = 11.0 Hz, 1H), 5.53 (dd, J = 15.5, 7.1 Hz, 1H), 5.40 (dt, J = 10.4, 4.8 Hz, 1H),), 4.41-4.25 (m, 2H), 4.06-4.01 (m, 1H), 2.69-2.62 (m, 1H), 2.56 (dd, J = 17.1, 4.4 Hz, 1H), 2.46 (dd, J = 17.1, 9.5 Hz, 1H), 2.26-2.21 (m, 1H), 1.75-1.61 (m, 4H), 0.89 (s, 9H), 0.08, 0.07 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 153.9, 133.2, 132.9, 128.5, 128.2, 87.7, 77.0, 72.9, 68.0, 29.0, 28.2, 26.7, 26.0, 25.6, 18.3, -4.3, -4.7; IR (film) ν_{max} 2954, 2929, 2857, 2238, 1716, 1245, 1110, 1075, 837; ESIMS *m/z* 357 ([M + Na^+], $C_{19}H_{30}NaO_3Si$ requires 357). HRMS(FAB^+) *m/z* 333.1888 ([M - H]$^+$, $C_{19}H_{29}O_3Si$ requires 333.1886).



13

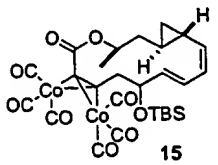
Diels-Alder product **13**. Cyclic alkyne **11** (27 mg, 0.081 mmol) and excess diene **12** (0.30 mL, 0.90 mmol) were mixed and heated in a sealed vial to 140 °C for 48.5 hours. The mixture was cooled to room temperature, loaded onto a PTLC plate, and purified (4:1 hexane/EtOAc) to afford aromatic product **13** (20 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.64, (s, 1H), 6.38 (dd, J = 15.4, 10.9 Hz, 1H), 6.35 (d, J = 2.6 Hz, 1H), 6.30 (d, J = 2.6 Hz, 1H), 6.23 (t, J = 10.6 Hz, 1H), 5.95 (s, 1H), 5.78 (dd, J = 15.3, 8.4 Hz, 1H), 5.60 (q, J = 9.9 Hz, 1H), 4.69 (q, J = 9.1 Hz, 1H), 4.12 (t, J = 8.5 Hz, 2H), 3.63 (d, J = 13.0 Hz, 1H), 2.62 (dd, J = 13.1, 8.9 Hz, 1H), 2.50-2.40 (m, 1H), 2.12-2.05 (m, 1H), 1.87-1.76 (m, 2H), 1.56-1.44 (m, 2H), 0.78 (s, 9H), -0.20, -0.25 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 172.2, 165.7, 160.3, 144.8, 135.4, 131.0, 129.9, 126.0, 113.0, 105.3, 102.2, 78.7, 64.3, 46.6, 25.9, 24.2, 23.7, 23.0, 18.4, -4.7,

-5.0; IR (film) ν_{max} 3380, 2954, 2929, 2856, 1648, 1620, 1254, 1169, 1106, 1061, 837; ESIMS *m/z* 441 ([M + Na^+], $C_{23}H_{34}NaO_5Si$ requires 441). HRMS (FAB^+) *m/z* 418.2173 ($[M]^+$, $C_{23}H_{34}O_5Si$ requires 418.2176).



14

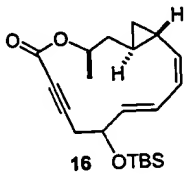
Cobalt complex **14**. To a solution of alkyne **8** (526 mg, 1.31 mmol) in toluene (60 mL) was added $Co_2(CO)_8$ (625 mg, 1.83 mmol). The mixture was stirred at room temperature for 30 min, and the solvent was removed under reduced pressure. The dark residue was purified by flash chromatography (silica, 0 to 5% EtOAc in hexane) to give cobalt complex **14** (902 mg, 100%) as an inseparable mixture of two diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, *J* = 15.3, 10.6 Hz, 1H), 6.03 (ddd, *J* = 15.3, 11.3 Hz, 1H), 5.68 (dd, *J* = 14.9, 6.9 Hz, 1H), 5.61 (dd, *J* = 15.2, 6.8 Hz, 1H), 5.38 (ddd, *J* = 17.1, 10.1, 8.7 Hz, 1H), 5.10 (q, *J* = 6.4 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.85 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.41, (m, 1H), 3.20-3.15 (m, 2H), 1.76 (d, *J* = 6.7 Hz, 3H), 1.59 (t, *J* = 6.6 Hz, 2H), 1.32 (d, *J* = 6.2 Hz, 3H), 1. 22-1.17 (m, 1H), 0.90 (s, 9H), 0.82-0.72 (m, 1H), 0.66-0.59 (m, 2H), 0.09, 0.08 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 198.7, 169.2, 141.4, 134.3, 132.5, 132.4, 132.2, 131.0, 130.2, 128.8, 127.2, 127.1, 112.0, 93.0, 81.0, 73.7, 73.6, 73.1, 40.0, 26.1, 22.4, 19.9, 18.6, 18.4, 17.4, 13.9, 13.5, -4.2, -4.3, -4.6; IR (film) ν_{max} 2956, 2930, 2858, 2097, 2058, 2029, 1703, 1221, 1065; ESIMS *m/z* 711 ([M + Na^+], $C_{30}H_{38}Co_2NaO_9Si$ requires 711).



15

RCM product **15**. To a solution of alkyne-cobalt complex **14** (67 mg, 0.097 mmol) in dry CH_2Cl_2 (485 mL) was added tricyclohexyl phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]

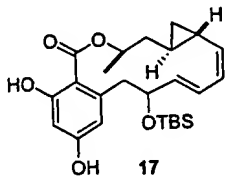
[bezylidene] ruthenim(IV) dichloride (second generation Grubbs catalyst) (21 mg, 0.025 mmol). The resulting mixture was heated to 45 °C for 1.5 hours, and filtered through a short column of silica gel. The filtrate was concentrated in vacuum. The residue was purified by PTLC (15:1 hexanes/EtOAc) to give cyclic product **15** as a 2:1 mixture of two separable diastereomers. Major isomer (23.1 mg, 37%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.49 (dd, J = 15.4, 10.9 Hz, 1H), 5.84 (t, J = 10.6 Hz, 1H), 5.50 (dd, J = 15.4, 8.5 Hz, 1H), 5.06 (dd, J = 10.5, 6.9 Hz, 1H), 5.02-4.94 (m, 1H), 4.81-4.75 (m, 1H). 3.48-3.36 (m, 2H), 2.22-2.25 (m, 1H), 1.58-1.50 (m, 1H), 1.50-1.46 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.90-0.80 (m, 1H), 0.89 (s, 9H), 0.67-0.63 (m, 1H), 0.59-0.55 (m, 1H), 0.12, 0.09 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 199.0, 170.4, 135.7, 134.9, 129.2, 127.8, 92.0, 77.5, 72.5, 72.1, 45.5, 38.0, 26.1, 10.3, 18.4, 16.4, 16.0, -4.2, -4.6; IR (film) ν_{max} 2955, 2928, 2854, 2097, 2060, 2029, 1692, 1232, 1056; ESIMS *m/z* 669 ([M + Na^+], $C_{27}H_{32}Co_2NaO_9Si$ requires 669); $[\alpha]^{25}_D$ -127 (*c* 0.11, $CHCl_3$). Minor isomer (12.6 mg, 20%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.60 (dd, J = 15.7, 9.9 Hz, 1H), 5.86 (t, J = 10.3 Hz, 1H), 5.81 (dd, J = 15.7, 4.4 Hz, 1H), 5.12-5.05 (m, 1H), 4.99 (t, J = 9.9 Hz, 1H), 4.46-4.44 (m, 1H), 3.58 (dd, J = 15.3, 9.4 Hz, 1H), 3.32 (dd, J = 15.3, 4.2 Hz, 1H), 2.16 (dt, J = 15.3, 4.2 Hz, 1H), 1.65-1.59 (m, 2H), 1.36 (d, J = 6.5 Hz, 3H), 0.94 (s, 9H), 0.64-0.59 (m, 2H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 198.6, 169.7, 135.9, 132.6, 126.8, 126.5, 92.0, 80.7, 73.4, 73.0, 41.8, 37.7, 26.1, 19.3, 18.5, 18.4, 15.1, 13.7, -4.5, -4.6; IR (film) ν_{max} 2929, 2856, 2097, 2059, 2028, 1702, 1220, 1059; ESIMS *m/z* 669 ([M + Na^+], $C_{27}H_{32}Co_2NaO_9Si$ requires 669). $[\alpha]^{25}_D$ +48 (*c* 0.19, $CHCl_3$).



16

Cyclic alkyne **16**. The major isomer of **15** (23.1 mg, 0.0358 mmol) was dissolved in dry THF (1 mL). At 0 °C, a solution of I_2 (135 mg, 0.536 mmol) in THF (5 mL) was added. After 35 minutes at 0 °C, the reaction was quenched by the addition of a 2 mL 1:1 mixture of sat. aqueous $Na_2S_2O_3$ and $NaHCO_3$,

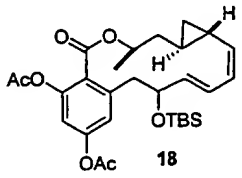
followed by warming to room temperature and diluting with EtOAc (20 mL). The layers were separated, and the organic layer was washed with sat. aqueous NH_4Cl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by PTLC (15:1, hexanes/EtOAc) to cyclic alkyne **16** as colorless oil (8.9 mg, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70 (dd, J = 15.6, 11.1 Hz, 1H), 5.98 (t, J = 10.8 Hz, 1H), 5.51 (dd, J = 15.6, 7.7 Hz, 1H), 5.20-5.14 (m, 1H), 4.92 (t, J = 10.7 Hz, 1H), 4.38-4.33 (m, 1H), 2.59 (dd, J = 16.8, 4.3 Hz, 1H), 2.41 (dd, J = 16.7, 10.9 Hz, 1H), 2.07 (dt, J = 14.8, 1.8 Hz, 1H), 1.74-1.67 (m, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.19-1.12 (m, 1H), 0.93-0.87 (m, 1H), 0.89 (s, 9H), 0.69-0.65 (m, 1H), 0.63-0.58 (m, 1H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 153.4, 136.5, 132.5, 128.3, 125.4, 85.7, 77.4, 73.8, 72.0, 38.6, 29.2, 26.0, 20.4, 18.4, 18.2, 14.6, 12.8; IR (film) ν_{max} 2954, 2928, 2856, 2238, 1706, 1252, 1105, 1072, 1004; ESIMS *m/z* 383 ([M + Na^+], $C_{21}H_{32}NaO_3Si$ requires 383); HRMS (FAB^+) *m/z* 360.2130 ($[M]^+$, $C_{21}H_{32}O_3Si$ requires 360.2121). $[\alpha]^{25}_D$ +56 (*c* 0.95, $CHCl_3$).



17

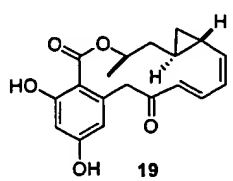
Diels-Alder product **17**. Compound **16** (156 mg, 0.43 mmol) was dissolved in diene **12** (0.75 mL, 2.3 mmol) and heated to 140 °C in a sealed vial for 66 hours. The reaction mixture was cooled to room temperature and purified by PTLC (4:1, hexanes/EtOAc) to give **17** (143 mg, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.58 (s, 1H), 6.56 (dd, J = 15.9, 9.3 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 5.94 (t, J = 9.5 Hz, 1H), 5.68 (dd, J = 15.9, 6.8 Hz, 1H), 5.46-5.43 (m, 1H), 5.34 (dd, J = 10.1, 4.3 Hz, 1H), 4.51 (q, J = 6.7 Hz, 1H), 3.79 (dd, J = 13.6, 6.2 Hz, 1H), 2.81 (dd, J = 13.1, 8.9 Hz, 1H), 1.99-1.81 (m, 2H), 1.44 (d, J = 6.5 Hz, 3H), 1.21-1.13 (m, 1H), 0.93-0.87 (m, 1H), 0.88 (s, 9H), 0.58-0.51 (m, 2H), -0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 164.8, 160.5, 143.8, 134.8, 133.7, 129.6, 128.0, 112.3, 106.1, 102.1, 75.7, 72.9, 42.6, 38.0, 26.1, 18.7, 18.4, 16.4, 16.1, 14.8, 1.4, -4.4, -4.6; IR (film) ν_{max} 3376,

2954, 2928, 2856, 1644, 1619, 1257, 1062, 835; ESIMS *m/z* 467 ([M + Na^+], $C_{25}H_{36}NaO_5Si$ requires 467). HRMS (FAB^+) *m/z* 444.2336 ([M]$^+$, $C_{25}H_{36}O_5Si$ requires 444.2332). $[\alpha]^{25}_D$ +3.1 (*c* 1.3, $CHCl_3$).



18

To a solution of **17** (243 mg, 0.546 mmol) in anhydrous DMF (13.5 mL) was added acetic anhydride (2.9 mL) and 4-(dimethylamino)pyridine (12.0 mg, 0.0546 mmol) sequentially. After 30 min at room temperature, the reaction was quenched by addition of 50 mL of pH 7.2 phosphate buffer. The resulting mixture was diluted with EtOAc (75 mL), separated and the aqueous layer was extracted with additional EtOAc (2 x 50 mL). The combined organic layers were washed with 5% aqueous NaCl (2 x 45 mL). The combined washings were extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aqueous NaCl (30 mL), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by PTLC (4:1 hexane/EtOAc) gave diacetate **18** (250 mg, 87%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.59 (dd, *J* = 16.0, 10.5 Hz, 1H), 5.89 (t, *J* = 10.5 Hz, 1H), 5.66 (dd, *J* = 16.1, 4.9 Hz, 1H), 5.26-5.23 (m, 2H), 4.51 (q, *J* = 5.8 Hz, 1H), 3.12-3.02 (m, 2H), 2.28, 2.23 (2s, 6H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.46-1.39 (m, 1H), 1.14 (ddd, *J* = 14.9, 10.1, 2.0 Hz, 1H), 0.96-0.87 (m, 1H), 0.87 (s, 9H), 0.52-0.48 (m, 2H), -0.01, -0.02 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 168.6, 168.4, 166.4, 151.4, 148.7, 139.1, 135.9, 133.6, 129.2, 127.2, 125.6, 120.4, 114.7, 73.8, 73.2, 43.2, 40.0, 26.0, 21.3, 21.0, 19.3, 18.3, 16.9, 16.2, 17.7, -4.6, -4.7; IR (film) ν_{max} 2954, 2928, 2856, 1775, 1720, 1612, 1191, 1134, 1069; ESIMS *m/z* 551 ([M + Na^+], $C_{29}H_{40}NaO_7Si$ requires 551); HRMS (FAB^+) *m/z* 528.2569 ([M]$^+$, $C_{29}H_{40}O_7Si$ requires 528.2543). $[\alpha]^{25}_D$ -38 (*c* 1.1, $CHCl_3$).

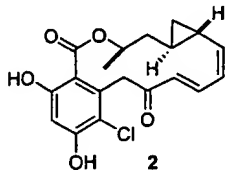


19

Cyclopropamonocillin **19**. To a solution of diacetate **18** (250 mg, 0.473 mmol) in THF (10.2 mL) at 0 °C was added pyridine (3.4 mL) and HF-Pyridine complex (1.7 mL) sequentially. The resulting mixture was stirred at room temperature for 10.5 hrs. TMSOMe (30 mL) was added, and stirring was continued for 45 min to quench the remaining HF. The solvents were removed under reduced pressure. The alcohol isolated was dried under high vacuum, and dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Dess-Martin periodinane (301 mg, 0.710 mmol) was added, and the resulting mixture was stirred at room temperature for 15 min. The solution was then directly loaded on PTLC plates and purified (1:1 hexane/EtOAc) to give the desired ketone (133 mg, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (dd, J = 16.1, 11.3 Hz, 1H), 6.97 (d, J = 1.4 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.20 (t, J = 10.4 Hz, 1H), 5.96 (d, J = 16.0 Hz, 1H), 5.60 (dd, J = 10.0, 7.2 Hz, 1H), 5.47-5.41 (m, 1H), 4.20 (d, J = 13.8 Hz, 1H), 3.77 (d, J = 13.8 Hz, 1H), 2.31 (dt, J = 15.3, 4.4 Hz, 1H), 2.25, 2.24 (2s, 6H), 1.73-1.71 (m, 1H), 1.50 (d, J = 6.5 Hz, 3H), 1.26-1.21 (m, 1H), 1.00-0.97 (m, 1H), 0.75-0.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 198.4, 168.5, 165.0, 152.1, 149.2, 145.6, 143.7, 135.7, 129.6, 128.8, 124.6, 119.1, 115.6, 72.8, 43.0, 38.3, 21.2, 18.2, 16.7, 16.5, 15.6; IR (film) ν_{max} 2928, 1774, 1728, 1657, 1621, 1586, 1290, 1190, 1132, 1029; ESIMS *m/z* 435 ([M + Na^+], $C_{23}H_{24}NaO_7$ requires 435); HRMS (FAB^+) *m/z* 413.1616 ([M + H]$^+$, $C_{23}H_{25}O_7$ requires 413.1600). $[\alpha]^{25}_D$ -269 (*c* 1.43, $CHCl_3$).

The above ketone (169 mg, 0.409 mmol) was dissolved in 26 mL 1:1 MeOH and 5% aqueous $NaHCO_3$, and stirred at room temperature for 14 hrs to remove the phenolic acetates. The resulting solution was diluted with sat. aqueous NH_4Cl (80 mL) and EtOAc (100 mL) and separated. The aqueous layer was extracted with additional EtOAc (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuum. Purification by PTLC (1:1 hexane/EtOAc) provided **19** (124 mg, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.33 (s, 1H), 8.36 (dd, J = 16.1, 11.7 Hz, 1H), 6.48 (d, J = 1.6 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.20 (t, J = 11.3 Hz, 1H), 6.01 (d, J = 15.9 Hz, 1H), 5.72 (dd, J = 9.8, 6.2 Hz, 1H), 5.49-5.45 (m, 1H), 5.32 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.7 Hz, 1H), 2.31 (dt, J = 15.8, 3.3 Hz, 1H), 1.61-1.55 (m, 1H), 1.55 (d, J = 6.7 Hz, 3H), 1.32-1.28 (m, 1H), 1.03-0.97 (m, 1H), 0.74-0.72

(m, 1H), 0.64-0.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 201.8, 170.1, 165.6, 161.6, 145.3, 139.2, 129.5, 128.5, 109.4, 104.5, 102.7, 73.5, 43.2, 27.6, 17.9, 17.2, 15.9, 13.9; IR (film) ν_{max} 3260, 1650, 1618, 1586, 1447, 1259, 1160, 1099, 996, 854; ESIMS *m/z* 351 ([M + Na^+], $C_{19}H_{20}NaO_5$ requires 351); HRMS (FAB^+) *m/z* 329.1382 ([M + H]$^+$, $C_{19}H_{21}O_5$ requires 329.1389). (+)-(*R, R, S*)-**19**: $[\alpha]^{25}_D$ -189 (*c* 0.77, CH_2Cl_2).



2

Cyclopropparadicicol **2**. Compound **19** (26.5 mg, 0.081 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. A solution of SO_2Cl_2 in CH_2Cl_2 (4.5 mL, diluted from 0.123 mL 1 M solution in CH_2Cl_2, 0.123 mmol) was added dropwise. After 45 minutes, the reaction was quenched by the addition of 5 mL of 5% NH_4Cl, and diluted with CH_2Cl_2. The layers were separated, and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuum. Purification of the residue by PTLC (3:1, hexanes/EtOAc) gave **2** as a white solid (17.8 mg, 61%). ^1H NMR ($CDCl_3$, 500 MHz) δ 10.89 (s, 1H), 8.00 (dd, *J* = 15.9, 11.3 Hz, 1H), 6.63 (s, 1H), 6.42 (s, 1H), 6.13 (t, *J* = 11.2 Hz, 1H), 6.04 (d, *J* = 16.3 Hz, 1H), 5.62 (dd, *J* = 9.9, 5.8 Hz, 1H), 5.46-5.42 (m, 1H), 4.90 (broad d, *J* = 15.9 Hz, 1H), 3.77 (bs, 1H), 2.22 (dt, *J* = 15.8, 3.2 Hz, 1H), 1.60-1.52 (m, 1H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.15-1.11 (m, 1H), 0.90-0.85 (m, 1H), 0.69-0.65 (m, 1H), 0.57-0.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 199.2, 169.4, 162.7, 155.6, 143.5, 142.5, 136.9, 129.9, 128.9, 115.6, 107.8, 103.5, 74.4, 46.4, 37.4, 17.9, 17.3, 15.6, 13.6; IR (film) ν_{max} 3341, 1716, 1651, 1609, 1578 cm^{-1}; ESIMS *m/z* 385 ([M + Na^+], $C_{19}H_{19}NaO_5Cl$ requires 385); HRMS (ESI) *m/z* 385.0820 ([M + Na^+], $C_{19}H_{19}NaO_5Cl$ requires 385.0819). (+)-(*R, R, S*)-**2**: $[\alpha]^{25}_D$ +69 (*c* 0.87, CH_2Cl_2).

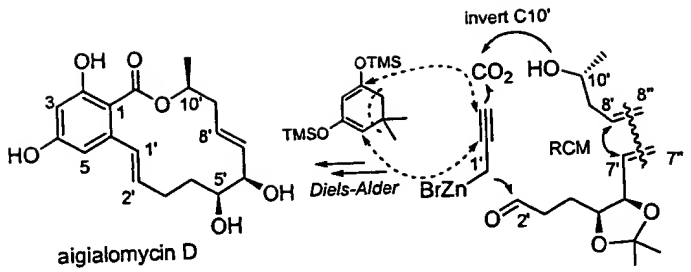
Total Synthesis of Aigialomycin D

Xudong Geng[†] and Samuel J. Danishefsky*[†‡]

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY 10027

s-danishefsky@ski.mskcc.org

ABSTRACT



The first total synthesis of resocinylic macrolide aigialomycin D was described. The resorcinylic moiety was constructed by a highly efficient Diels-Alder reaction using a disiloxydiene and a 14-membered "ynolide" as the dienophile synthesized by ring-forming olefin metathesis.

There are many natural products, usually bacterial metabolites, featuring a macrolide fused to a monocyclic benzenoid matrix, bearing a resorcinol-like substitution pattern. Not infrequently, the resorcinol moiety carries additional functionality, resulting in higher levels of oxidation. Natural products in this family (*cf. inter alia* radicicol,[1] LL-Z-1640s,[2] monocillins,[3] nordinone[4] and zearelenone[5]) possess potentially exploitable patterns of antitumor, antibiotic and antimalarial activity. Indeed, we were first attracted to this structural series by radicicol[1,6] – a non quinoidal inhibitor of the key molecular chaperone HSP90. Using radicicol (2) as a lead compound, we were soon led to cyclopropradicicol (3)[7] as a potentially valuable analog structure, wherein the cyclopropane simulates the conformational consequences of the epoxide, without the liabilities associated with a potentially labile alkylation site. Indeed, xenograft studies suggest that cyclopropradicicol (3) may well be a superior drug relative to radicicol (2).[8] The promise of cyclopropradicicol, albeit in an early preclinical setting, as well as the structural diversity encountered in this family of bioactive molecules, prompted us to explore new strategies for building such compounds in the laboratory. Indeed, a new strategy was described to reach cyclopropradicicol.[9]

Recently, five new 14-membered resorcyclic macrolides, termed aigailomycins A-E, were isolated from the marine

† Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research.

‡ Columbia University.

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mangrove fungus *Aigialus parvus* BCC5311.[10] Among those compounds, aigialomycin D (**1**) (Figure 1) exhibited potent antimalarial activity (IC_{50}: 6.6 μg/mL against *P. falciparum*) and antitumor activity (IC_{50}: 3.0 μg/mL against KB cells).[10]

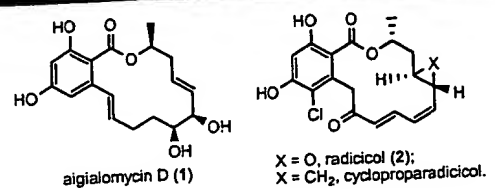


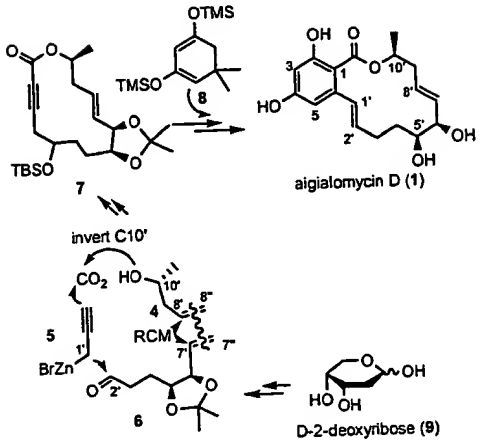
Figure 1. Resorcinylic macrolides: Aigialomycin D, radicicol and cyclopropparadicicol.

Not surprisingly, our first thought was to use the synthetic paradigm developed for cyclpropparadicicol.[9] However, unlike **3**, **1** does not, in the end, contain benzylic oxygen functionality. Rather, it contains a 1', 2' styrene-like double bond, ortho to the acyloxyl group of the lactone. It was our plan to install this double bond by β-elimination of a C2' leaving group toward the benzo domain (*vide infra*). To bring about a pre-elimination setup, the initial bond formation would be between future carbons 1' and 2'. The more serious incremental complexity in the aigialomycin series arises from the two hdyroxy – bearing stereogenic centers at C5' and C6' in allylic and homoallylic relationships respectively to the C7' – C8' double bond. The thought was to construct this double bond by ring forming olefin metatheses via extrusion of carbons 7" and 8". Scheme 1 sets forth the thinking that led to a remarkably straightforward total synthesis of agialomycin D.

It was recognized that, if properly managed, the functionality present in the readily available D-2-deoxyribose (**9**) could lead to a functional equivalent of the key proposed formal building block **6**. Compound **6** would not be used as such (*vide infra*).

In the event, the secondary hydroxyl groups at C3 and C4 of **9**, were engaged in an isopropylidene linkage (see **10**,[11] Scheme 2). The masked aldehyde character of C1 of the pentose could be exploited in the context of a Wittig protocol. The primary alcohol in the resultant product, **11**, was protected as its pivaloyl derivative (see **12**). In this compound, the primary methylene group bearing the pivaolyloxy group would emerge as C7' of the ring closing metathesis (RCM) precursor (*vide infra*). Hydroboration of **12** followed by oxidation, as shown, led us to **13** which, following oxidation of its primary alcohol function, delivered **14**.

Scheme 1. Synthetic Strategy.



Chain extension of the aldehyde by propargylation afforded **15** as a mixture of stereoisomers. In this compound, as well as in subsequent *seco* intermediates, these stereoisomers manifested nearly identical chromatographic characteristics. Thus, the mixtures were treated as single entities in the progression until compound **23**. The secondary hydroxyl groups in epimers **15** were protected as t-butyldimethyl silyl ethers (see **16**), thus enabling installation of a vinyl group, destined to serve as the C7'- C7" moiety in the eventual RCM (see steps leading to **18**).

Carboxylation of the ethynyl group in **18** occurred smoothly to afford carboxylic acid **19**. The latter reacted with *R* alcohol **4**, giving rise, through a Mitsunobu protocol, to the *S*-ester **20**, still bearing epimeric OTBS ethers at the future carbon **2'**.

Our previous experience[9] had prepared us well for accomplishing the much needed ring closing metathesis reaction. First, it would be necessary to immobilize the ethynyl linkage in **20** as its dicobalt hexacarbonyl complex (Scheme 3).[9,12] This step accomplishes two objectives. First, the acetylene function is insulated from diversion to an ene-yne metathesis format. Furthermore, it is likely that the formation of the complex modifies the angles of the ethynyl sector,[13] such as to bring carbons 7' and 8' into closer proximity. In the event, the hexacarbonyl complex **21** was obtained in 94% yield. Ring closing metathesis was easily accomplished, using the recently published catalysis methodology from the Grubbs group.[14] The 14 membered macrolide (**23**) was thus in hand. At this stage the two

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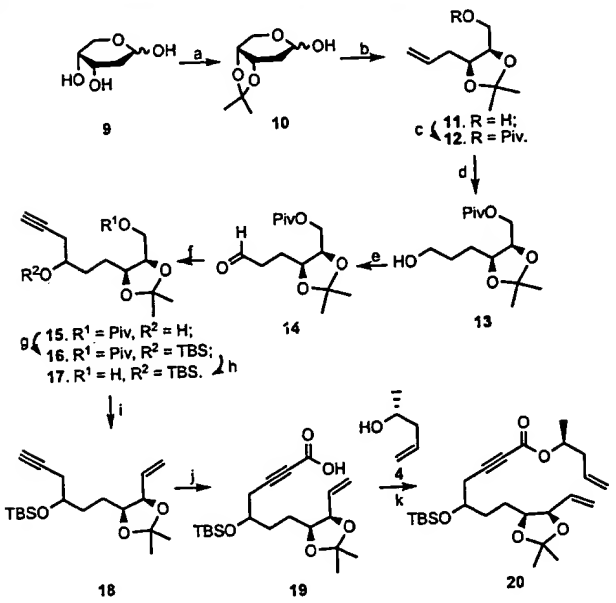
stereoisomeric products were easily separated by chromatography to provide the individual compound(s) at a 1.2:1 ratio (stereochemistry not rigorously assigned). We note that in each diastereomer, only the *E* configured double bond was obtained (J ≅ 15.2 Hz).

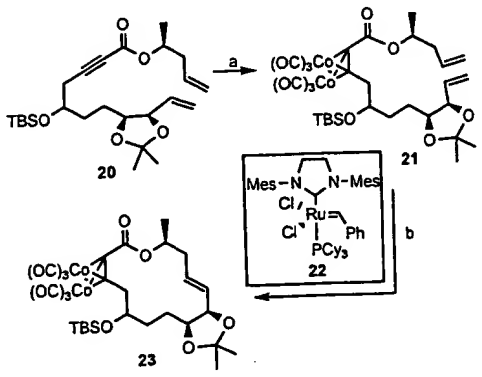
Scheme 2. Synthesis of diene **20**.



a) 2-methoxypropene, *p*-TSA, DMF, 3 h, 62%; b) KHMDS, $Ph_3P^+CH_3I^-$, THF, -78 °C to r.t., 10 h, 68%; c) PivCl, Et_3N, DMAP, CH_2Cl_2, 10 h, 90%; d) 9-BBN, THF, 0 °C to r.t., 4 h, then NaOH, H_2O_2, H_2O, 2.5 h, 88%; e) SO_3-Pyr., DMSO, CH_2Cl_2, Et_3N, 0 °C, 1 h; f) propargyl bromide, zinc, THF, 0 °C, 2 h; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 10 h, 89% from **13**; h) NaOMe/MeOH, 10 h, 88%; i) SO_3-Pyr., DMSO, CH_2Cl_2, Et_3N, 0 °C, 2 h, then KHMDS, $Ph_3P^+CH_3I^-$, THF, -78 °C to r.t., 10 h, 86% for two steps; j) BuLi, dry ice, -78 °C to r.t., 2 h; k) **4**, DIAD, PPh_3, tol., 10 h, 85% for two steps.

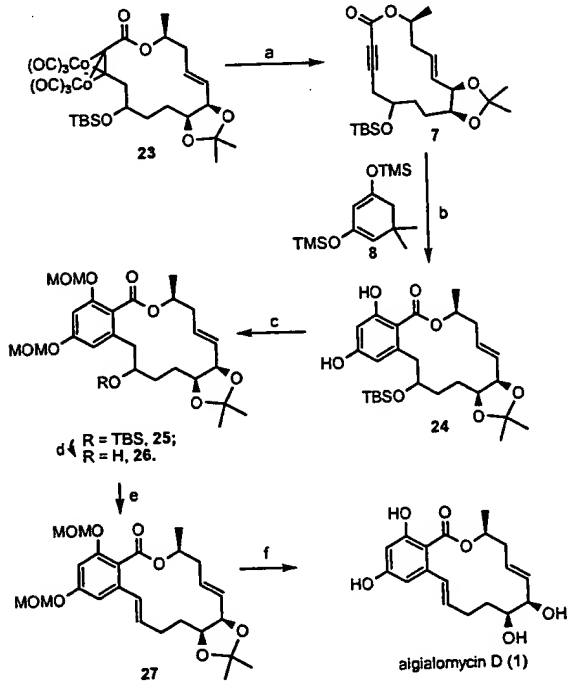
Decomplexation of the two separated compounds **23a** and **23b**, using standard conditions, thereby afforded "ynolide" epimers **7** (Scheme 4). Each stereoisomer was subjected to Diels Alder reaction with the disiloxydiene **8**, following previously developed conditions.[9] In the event, cycloaddition followed by extrusion of isobutylene occurred smoothly affording macrolides **24a** and **24b**. It proved useful to protect the two resorcynilic hydroxyl groups in the form of their MOM derivatives (see **25a** and **25b**) before proceeding with installation of the styrene like double bond. At this stage, deprotection of the silyl group was accomplished through the agency of HF-pyridine. Indeed, dehydration of the resulting alcohol functions in **26a** and **26b**, each using Martin's sulfurane conditions,[15] resulted in installation of the C1'-C2' double

Scheme 3. Synthesis of macrolactone **23** through RCM.



a) $Co_2(CO)_8$, tol., 30 min, 94%; b) 2nd generation Grubbs catalyst (25 mol%), CH_2Cl_2, 10 h, **23A**, 38%; **23B**, 42%.

Scheme 4. Completion of the total synthesis of aigialomycin D.



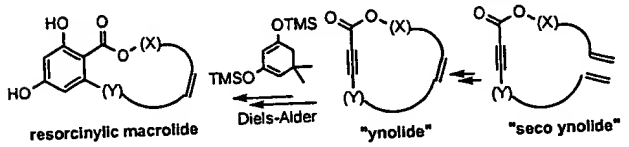
a). CAN, acetone, -10 °C, 15 min, **7A**, 94%; **7B** 95%; b). **8** neat, 140 °C, 36 h, **24A**, 74%; **24B**, 84%; c) MOMCl, DIPEA, CH_2Cl_2, 10 h, **25A**, 78%; **25B**, 83%; d) HF-pyr., pyr., THF, 10 h, **26A**, 78%; **26B**, 87%; e) $[PhC(CF_3)_2O]_2SPh_2$, CH_2Cl_2, 0 °C to r.t., 2 h, from **26A** to **27**, 90%; from **26B** to **27**, 84%; f) 0.5 N HCl, H_2O/MeOH, 2 d, 69%.

(15) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327-4329.

bond with the formation of the identical product, **27**. Global acidic deprotection of the two MOM functions and the acetonide (0.5 N HCl) served to complete the first total synthesis of aigialomycin D (**1**). The assignment of structural and relative configuration could well have been rigorously accomplished based on our measurements (proton NMR, carbon NMR, mass spec and IR) accumulated on the fully synthetic material. In the case at hand, further support comes from the very close correspondence of our data with those previously reported for the target structure aigialomycin D.[10]

The synthesis described above, serves to further demonstrate the adaptability and generalizability of the basic protocol ("seco ylolide" → "ylolide" → resorcinylic macrolide, see Scheme 5). The total synthesis of **1** was accomplished in 18 steps in an overall yield of approximately 8%. We note in passing that compound **1** does bind to HSP90 (though significantly less so than radicicol (**2**)[16]). It will be interesting to attempt to utilize this newly acquired and highly concise route to matrices resembling radicicol for the purposes of discovering new and superior agents based on the theme of HSP90 inhibition.

Scheme 5. "Ynolide" synthetic protocol.



Acknowledgment. Support for this research was provided by the National Institute of Health (CA28824). Dr. Geoge Sukenic and Ms. Anna Dudkina are acknowledged for NMR and mass pectro-metric analysis. We thank Drs. Zhi-Qiang Yang and William Berkowitz for helpful discussions.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Geng, X.; Chiosis, G.; Danishefsky, S. J. unpublished results.

Supporting Information:

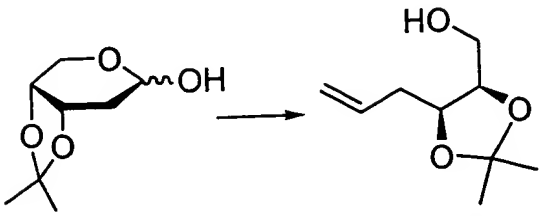
Total Synthesis of Aigialomycin D.

Xudong Geng and Samuel J. Danishefsky*

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY, 10027
s-danishefsky@ski.mskcc.org

General Methods: Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. THF, toluene, and methylene chloride was obtained from a dry solvent system (passed through a prepacked column of alumina) and used without further drying. All air and water sensitive reactions were performed in flame-dried glassware under a positive pressure of prepurified argon gas. NMR (^{1}H and ^{13}C) spectra were recorded on Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz as noted individually, referenced to $CDCl_3$ (7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C) or CD_3COCD_3 (2.09 ppm for ^{1}H and 30.6 and 205.9 ppm for ^{13}C). Infrared spectra (IR) were obtained on a Perkin-Elmer FT-IR model 1600 spectrometer. Melting point was tested on a electrothermal series IA9100 digital melting point apparatus. Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds which were not UV active were visualized by dipping the plates in para-anisaldehyde solution and heating. Preparative thin layer chromatography was performed using the

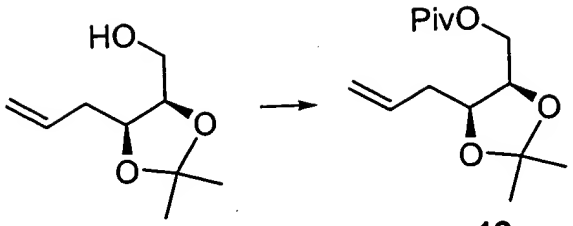
indicated solvent on Whatman® (LK6F Silica gel 60 Å 250 μM or Pk6F Silica Gel 60 Å 1000 μM) TLC plate.



10 11

(*2R, 3S*)-Hex-5-ene-1,2,3-triol 2,3-acetonide (11):

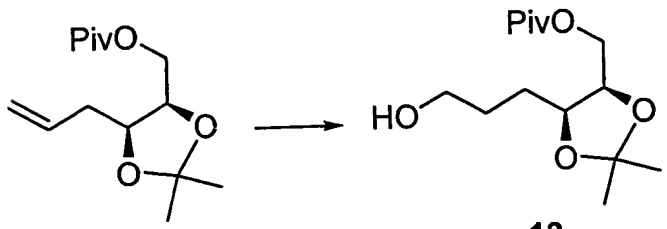
To a stirring suspension of $Ph_3P^+CH_3I^-$ (11.2 g, 27.7 mmol) in 30 mL THF was added KHMDS (0.5 M in toluene, 46.0 mL, 23.0 mmol) at -78 °C. The solution was warmed up to 0 °C and stirred for 30 min before cooled down to -78 °C. Acetonide **10**[1] (1.6 g, 9.2 mmol) in 5 mL THF was added via cannula and the solution was warmed up to r.t. overnight (10 h) before quenched with saturated aqueous NH_4Cl solution, extracted with EtOAC (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (4/1) as the eluant to afford **11** as a colorless oil (1.02 g, 68%). $[\alpha]_D^{25}$ 54.8 (*c* 0.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.46 (s, 3 H), 2.02 (b, 1 H), 2.25-2.32 (m, 1 H), 2.37-2.44 (m, 1 H), 3.65 (m, 1 H), 4.16-4.21 (m, 1 H), 4.24-4.28 (m, 1 H), 5.10-5.18 (m, 2 H), 5.79-5.89 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 28.1, 33.6, 61.6, 76.2, 77.8, 108.3, 117.3, 134.2. LRMS (ESI) calcd for $C_9H_{16}O_3Na^+$ $[M+Na]^+$: 195.1, found 194.9. LRMS (ESI) calcd for $C_9H_{16}O_3Cl^-$ $[M+Cl]^-$: 207.1, found 207.1.



11 12

Pivalate (12):

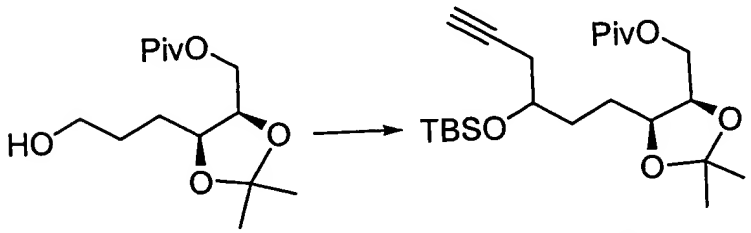
To a solution of **11** (752 mg, 4.37 mmol), DMAP (106 mg, 0.874 mmol) and triethylamine (2.5 ml, 17.5 mmol) in CH_2Cl_2 (8 ml) was added PivCl (1.1 ml, 8.74 mmol) at 0 °C. The reaction mixture was warmed up to r.t. overnight (10h) before quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAC (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using hexanes/EtOAc (4/1) as the eluant to afford **12** as a colorless oil (984 mg, 90%). $[\alpha]_D^{25}$ 15.6 (*c* 0.32, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 1.33 (s, 3 H), 1.47 (s, 3 H), 2.28-2.41 (m, 2 H), 4.10-4.13 (m, 2 H), 4.22-4.29 (m, 2 H), 5.10-5.17 (m, 2 H), 5.81-5.91 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.5, 28.4, 39.1, 63.2, 75.5, 77.8, 108.8, 117.7, 134.6, 178.5. LRMS (ESI) calcd for $C_{14}H_{24}O_4Na^+$ $[M+Na]^+$ 279.2, found 278.9.



12 13

Alcohol **13**:

To a solution of **12** (166 mg, 0.648 mmol) in THF (1.5 mL) was added 9-BBN (0.5 M in THF, 2.8 mL, 1.425 mmol) at 0 °C. The reaction mixture was warmed up to r.t. over 4 h and H_2O (0.1 mL), NaOH (3 M, 0.7 mL) and H_2O_2 (30%, 0.2 mL) were added. The reaction mixture was diluted with H_2O 2.5 h later and acidified with citric acid (5%) till pH = 7. The mixture was extracted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, H_2O and brine. The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether /EtOAc (1/1) as the eluant to afford **13** as a colorless oil (156 mg, 88%). $[\alpha]_D^{25}$ 82.4 (*c* 0.07, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9 H), 1.36 (s, 3 H), 1.46 (s, 3 H), 1.59-1.80 (m, 4 H), 2.30 (b, 1 H), 3.54 (m, 2 H), 4.08 (dd, J = 6.1, 11.5 Hz, 1 H), 4.12 (dd, J = 5.6, 11.5 Hz, 1 H), 4.19 (m, 1 H), 4.25 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 25.9, 27.1, 28.0, 29.9, 38.7, 62.3, 62.9, 75.3, 77.0, 108.3, 178.2. HRMS (ESI) calcd for $C_{14}H_{26}O_5Na^+$ $[M+Na]^+$ 297.1678, found 297.1660, Δ = -6.0 ppm.



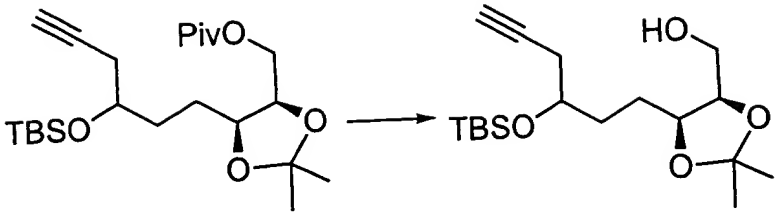
13 **16**

Alkyne 16:

To a solution of **13** (682 mg, 2.485 mmol) in CH_2Cl_2 (5 mL), DMSO (5 mL) and Et_3N (3 mL) was added SO_3-pyridine complex (1.6 g, 10.2 mmol) at 0 °C. The reaction mixture was stirred for 1 h before diluted with EtOAc and washed with HCl (0.5 *N*), H_2O,

saturated aqueous $NaHCO_3$ solution and brine. The organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The crude aldehyde **14** was used directly for next step without any further purification.

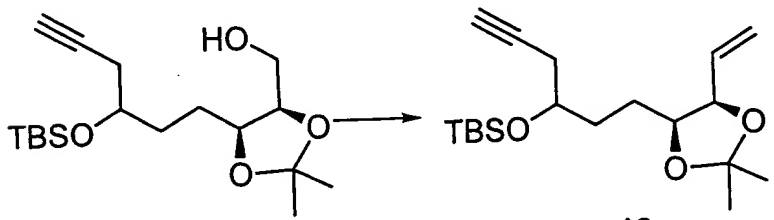
To a suspension of Zn (Nano-size power, pre-activated, 390 mg, 5.949 mmol) in THF (10 mL) was added propargyl bromide (80% in toluene, 0.53 mL, 4.759 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and a solution of aldehyde **14** thus obtained in THF (5 mL) was added and reaction mixture was warmed up to r.t. over 2 h before quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. To a solution of crude alcohol **15** thus obtained and 2,6-lutidine (0.6 mL, 4.76 mmol) in CH_2Cl_2 (8 mL) was added TBSOTf (0.82 mL, 3.57 mmol) and the reaction mixture was stirred for 10 h before quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (20/1) as the eluant to afford **16** as a colorless oil (896 mg, 89% from **13**). ^1H NMR (400 MHz, $CDCl_3$) δ -0.02-0.05 (m, 6 H), 0.80 (s, 9 H), 1.13 (s, 9 H), 1.26 (s, 3 H), 1.36 (s, 3 H), 1.42-1.74 (m, 4 H), 1.81 (m, 1 H), 2.22-2.29 (m, 2 H), 3.78 (m, 1 H), 4.01-4.08 (m, 3 H), 4.12-4.17 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 18.1, 24.3, 24.7, 25.6, 25.8, 27.0, 27.1, 27.2, 28.06, 28.07, 33.2, 33.3, 38.7, 62.8, 62.9, 70.1, 70.2, 70.4, 70.5, 75.2, 76.1, 77.1, 81.2, 108.20, 108.24, 178.1. HRMS (FAB) calcd for $C_{23}H_{42}O_5SiH^+$ $[M+H]^+$: 427.2880, found 427.2880, Δ = -0.1 ppm.



16 17

Alcohol 17:

To a solution of **16** (124 mg, 0.291 mmol) in MeOH (6 mL) was added NaOMe/MeOH (25%, 0.2 mL) and the reaction mixture was stirred for 10 h before quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (8/1) as the eluant to afford **17** as a colorless oil (87 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ -0.02-0.00 (m, 6 H), 0.80 (s, 9 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.32-1.91 (m, 4 H), 1.90 (m, 1 H), 1.96 (b, 1 H), 2.23-2.31 (m, 2 H), 3.53 (m, 2 H), 3.75 (m, 1 H), 4.08 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.6, -4.5, 18.0, 24.5, 24.7, 25.5, 25.6, 25.8, 27.2, 27.4, 28.2, 33.2, 33.4, 61.7, 70.1, 70.2, 70.46, 70.52, 76.9, 77.0, 77.9, 81.16, 81.24, 108.08, 108.14. HRMS (FAB) calcd for $C_{18}H_{34}O_4SiH^+$ $[M+H]^+$: 343.2305, found 343.2305, Δ = -0.1 ppm.

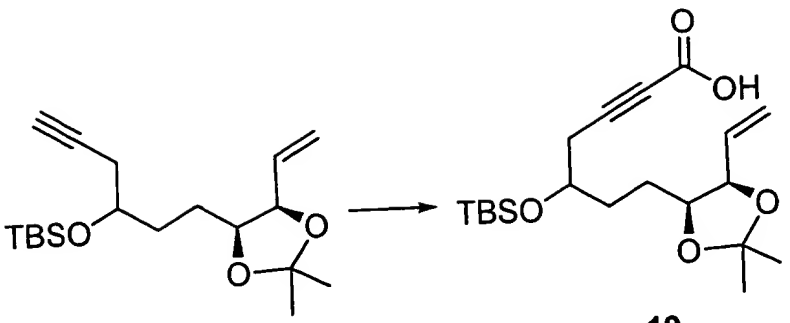


17 18

Enyne 18:

To a solution of **17** (87 mg, 0.254 mmol) in DMSO (1.0 mL), CH_2Cl_2 (1.0 mL) and Et_3N (1.0 mL) was added SO_3-Pyrdine complex (200 mg, 2.032 mmol) at 0 °C. The reaction mixture was stirred for 2 h before diluted with EtOAc and washed with HCl (0.5 *N*), H_2O, saturated aqueous $NaHCO_3$ solution and brine. The organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The crude aldehyde was used directly for next step without any further purification.

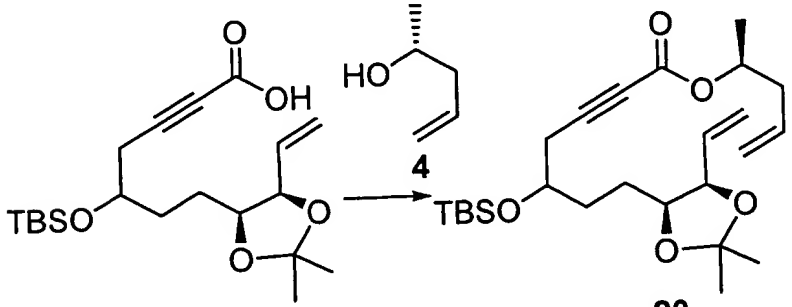
To a stirring suspension of $Ph_3P^+CH_3I^-$ (204 mg, 0.505 mmol) in 3 mL THF was added KHMDS (0.5 M in toluene, 0.9 mL, 0.454 mmol) at -78 °C. The solution was warmed up to 0 °C and stirred for 30 min before cooled down to -78 °C. Aldehyde obtained as mention above in 2 mL THF was added via cannula and the solution was warmed up to r.t. overnight (10 h) before quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (40/1) as the eluant to afford **18** as a colorless oil (73 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 3 H), 0.02 (s, 3 H), 0.83 (s, 9 H), 1.27 (s, 3 H), 1.43 (s, 3 H), 1.43-1.78 (m, 4 H), 1.92 (b, 1 H), 2.23-2.31 (m, 2 H), 3.76 (m, 1 H), 4.05-4.10 (m, 1 H), 4.43-4.45 (m, 1 H), 5.02-5.05 (m, 2 H), 5.71-5.80 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.30, -4.11, 18.4, 26.0, 26.1, 26.2, 26.5, 26.8, 27.7, 27.8, 28.62, 28.64, 33.2, 33.6, 70.4, 70.5, 71.07, 71.13, 78.6, 78.8, 80.2, 81.78, 81.82, 108.5, 118.6, 118.7, 134.7, 134.9. HRMS (FAB) calcd for $C_{19}H_{34}O_3SiNa^+$ $[M+Na]^+$: 361.2175, found 361.2175, Δ = 0.0 ppm.



18 19

Acid 19:

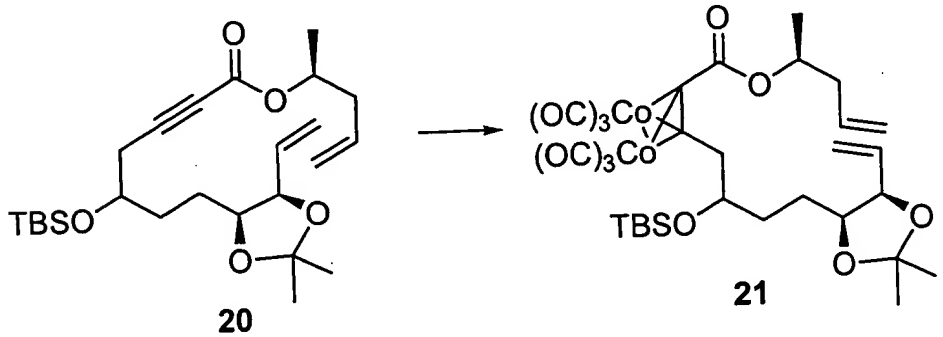
To a solution of **18** (586 mg, 1.731 mmol) in Et_2O (16 mL) was added BuLi (1.6 M in hexane, 1.817 mmol) at -78 °C and stirred for 5 min before quenched with dry ice and warmed up to r.t. The reaction mixture was washed with NaOH (0.1 M) and the aqueous layers were combined and acidified by HCl (0.1 M) until the pH = 2. The aqueous layer was extracted with EtOAc and the organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum and dried on high vacuum. ^1H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 3 H), 0.00 (s, 3 H), 0.79 (s, 9 H), 1.17 (s, 3 H), 1.40 (s, 3 H), 0.95-1.68 (m, 4 H), 2.38-2.39 (m, 2 H), 3.80 (b, 1 H), 4.06 (m, 1 H), 4.43 (m, 1 H), 5.14-5.36 (m, 2 H), 5.67-5.76 (m, 1 H), 10.5 (bs, 1 H). This crude was used directly for next step without any further purification.



19 20

Ester 20:

To a solution of acid **19** (249 mg, 0.651 mmol) in toluene (15 mL) was added alcohol **4** (0.081 mL, 0.781 mmol), PPh_3 (205 mg, 0.781 mmol), DIAD (0.154 mL, 0.781 mmol). The reaction mixture was stirred for 10 h and the solvent was removed under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (40/1) as the eluant to afford **20** as a colorless oil (255 mg, 85% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.06-0.00 (m, 6 H), 0.80 (s, 9 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.28 (s, 3 H), 1.38 (s, 3 H), 1.44-1.54 (m, 4 H), 2.20-2.24 (m, 1 H), 2.237-2.31 (m, 1 H), 2.35-2.37 (m, 2 H), 3.78-3.81 (m, 1 H), 4.03-4.05 (m, 1 H), 4.40-4.43 (m, 1 H), 4.94-4.96 (m, 1 H), 5.00-5.04 (m, 2 H), 5.14 (m, 1 H), 5.22 (dd, J = 6.7, 7.1 Hz, 1 H), 5.67-5.72 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.64, -4.58, -4.55, 0.0, 18.0, 19.3, 25.6, 25.7, 25.8, 26.1, 26.3, 27.6, 27.7, 28.2, 28.3, 33.3, 33.6, 40.0, 70.10, 70.12, 72.0, 74.9, 78.1, 78.3, 79.80, 79.82, 86.1, 108.2, 108.3, 118.1, 118.3, 118.4, 133.2, 134.2, 134.4, 153.2. HRMS (FAB) calcd for $C_{25}H_{42}O_5SiH^+$ $[M+H]^+$: 451.2880, found 451.2881, Δ = -0.3 ppm.

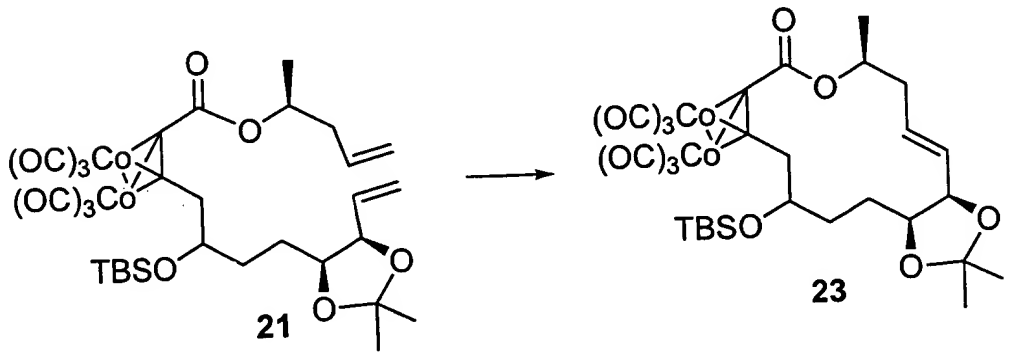


20 **21**

Cobalt-complex 21:

To a solution of **20** (20 mg, 0.044 mmol) in toluene (2.5 mL) was added $Co_2(CO)_8$ (21.2 mg, 0.062 mmol). The reaction mixture was stirred for 30 min before filtered through

neutral alumina and concentrated under reduced pressure vacuum. The residue was purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000 μM) using Hexanes/EtOAc (20/1) as the eluant to afford **21** as a purple oil (30 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07-0.09 (m, 6 H), 0.90 (s, 9 H), 1.30 (d, J = 8.1 Hz, 3 H), 1.33 (s, 1.6 H), 1.34 (s, 1.4 H), 1.45 (s, 1.6 H), 1.47 (s, 1.4 H), 1.25-1.46 (m, 1 H), 1.58-1.89 (m, 2.5 H), 1.89-1.95 (m, 0.5 H), 2.37-2.40 (m, 2 H), 3.00-3.12 (m, 2 H), 3.82-3.86 (m, 1 H), 4.08-4.14 (m, 1 H), 4.47-4.51 (m, 1 H), 5.07-5.14 (m, 3 H), 5.21 (d, J = 10.4 Hz, 1 H), 5.29 (d, J = 17.1 Hz, 1 H), 5.73-5.84 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 19.4, 25.6, 25.8, 26.5, 27.0, 28.16, 28.2, 32.7, 33.0, 40.3, 41.9, 42.1, 71.9, 72.8, 73.0, 78.2, 169.0, 197. HRMS (FAB) calcd for $C_{31}H_{42}Co_2O_{11}SiH^+$ $[M+H]^+$: 737.1239, found 737.1240, Δ = -0.2 ppm.

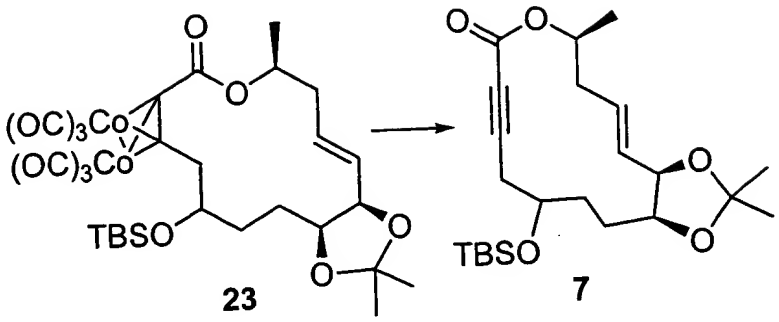


Macrolactone 23:

To a solution of **21** (339 mg, 0.460 mmol) in CH_2Cl_2 (80 mL) was added 2nd generation Grubbs catalyst (97 mg, 0.115 mol) in CH_2Cl_2 (15 mL) via cannula at r.t. The reaction mixture was stirred overnight and then the solvent was removed under reduced pressure vacuum and residue purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000

μM) using Hexanes/EtOAc (10/1) as the eluant to afford **23A** as a purple oil (123 mg, 38%). $[\alpha]_D^{25}$ -44.7 (*c* 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.35 (s, 3 H), 1.45 (s, 3 H), 1.39-1.59 (m, 2 H), 1.65-1.72 (m, 1 H), 1.93-1.97 (m, 1 H), 2.22-2.31 (m, 1 H), 2.42 (dt, *J* = 12.9, 1.83 Hz, 1 H), 3.08 (dd, *J* = 16.0, 1.5 Hz, 1 H), 3.23 (dd, *J* = 16.0, 9.4 Hz, 1 H), 3.92-3.95 (m, 1 H), 4.01-4.06 (m, 1 H), 4.40 (dd, *J* = 9.4, 5.7 Hz, 1 H), 5.53 (ddd, *J* = 15.2, 10.9, 1.52 Hz, 1 H), 5.72 (ddd, *J* = 15.2, 10.7, 3.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, -4.4, 18.5, 21.2, 23.1, 26.1, 26.2, 28.8, 30.5, 41.0, 42.7, 71.6, 71.8, 79.3, 80.0, 81.3, 92.9, 108.1, 129.1, 132.6, 169.9, 198.8. HRMS (FAB) calcd for $C_{29}H_{38}Co_2O_{11}SiH^+$ $[M+H]^+$: 709.0926, found: 709.0924, Δ = 0.2 ppm.

23B (136 mg, 42%). $[\alpha]_D^{25}$ -5.9 (*c* 0.27, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.15 (s, 3 H), 0.93 (s, 9 H), 1.32 (d, *J* = 6.3 Hz, 3 H), 1.35 (s, 3 H), 1.42 (s, 3 H), 1.11-1.54 (m, 2 H), 1.67 (m, 1 H), 1.88-1.93 (m, 1 H), 2.24-2.33 (m, 1 H), 2.41-2.45 (m, 1 H), 3.05 (dd, *J* = 14.9, 9.5 Hz, 1 H), 3.18 (dd, *J* = 14.9, 2.4 Hz, 1 H), 3.54-3.59 (m, 1 H), 4.03-4.09 (m, 1 H), 4.42 (dd, *J* = 9.5 Hz, 6.0 Hz, 1 H), 5.28 (m, 1 H), 5.53 (ddd, *J* = 15.2, 7.9, 4.0 Hz, 1 H), 5.77 (ddd, *J* = 15.2, 10.5, 3.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3, -4.0, 18.4, 21.1, 25.8, 26.1, 26.2, 26.3, 26.9, 28.6, 32.4, 40.7, 44.6, 71.8, 73.8, 78.6, 79.8, 81.1, 93.3, 107.9, 128.6, 133.6, 169.6, 198.6. HRMS (FAB) calcd for $C_{29}H_{38}Co_2O_{11}SiH^+$ $[M+H]^+$: 709.0926, found: 709.0924, Δ = 0.2 ppm.



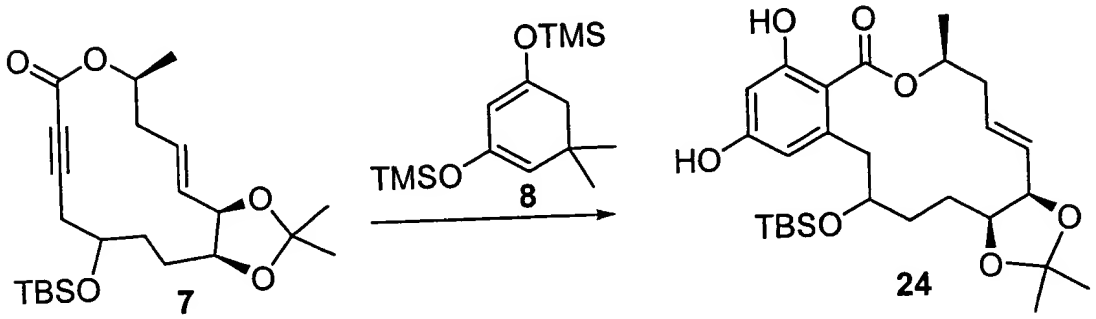
23 7

Macrolide 7:

To a solution of **23A** (123 mg, 0.174 mmol) in acetone (10 mL) was added CAN (475 mg, 0.868 mmol) at -10 °C. After 20 min, the reaction mixture was filtered through neutral alumina and the solvent was removed under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc (20/1) as the eluant to afford **7A** as a colorless oil (69 mg, 94%). $[\alpha]_D^{25}$ -124.6 (*c* 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ -0.06, (s, 3 H), 0.00 (s, 3 H), 0.81 (s, 9 H), 1.24 (d, J = 6.2 Hz, 1 H), 1.33, (s, 3 H), 1.40 (s, 3 H), 1.59-1.81 (m, 4 H), 2.18-2.22 (m, 1 H), 2.28-2.31 (m, 1 H), 2.34-2.45 (m, 2 H), 3.90-3.93 (m, 1 H), 3.98-4.01 (m, 1 H), 4.33-4.36 (m, 1 H), 4.83-4.87 (m, 1 H), 5.42-5.53 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8,18.4, 20.6, 26.1, 26.3, 28.4, 28.8, 30.1, 36.5, 40.6, 70.0, 71.7, 78.9, 80.1, 88.5, 108.7, 129.7, 132.0, 153.8.

7B was prepared by same procedure from **23B**. **7B**: (81 mg, 95%). $[\alpha]_D^{25}$ -173.3 (*c* 0.41, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.00, (s, 3 H), 0.01 (s, 3 H), 0.81 (s, 9 H), 1.26 (d, J = 6.1 Hz, 3 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.53-1.59 (m, 2 H), 1.77-1.81 (m, 2 H), 2.19-2.24 (m, 1 H), 2.24-2.26 (m, 1 H), 2.31-2.47 (m, 2 H), 3.80 (b, 1 H), 3.91-3.93 (m, 1 H), 4.34-4.40 (m, 1 H), 4.75-4.78 (m, 1 H), 4.82-4.86 (m, 1 H), 5.43-5.60 (m, 2 H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ -5.0, -4.8, 17.9, 20.17, 20.24, 25.5, 25.6, 25.7, 25.9, 28.0, 28.2, 28.3, 28.4, 29.6, 36.0, 36.7, 40.0, 40.1, 69.5, 70.8, 71.2, 71.4, 78.5, 78.6, 79.4, 79.6, 78.8, 108.2, 129.2, 131.3, 153.0. HRMS (FAB) calcd for $C_{25}H_{42}O_5SiNa^+$ $[M+Na]^+$: 473.2699, found: 473.2700, Δ = 0.2 ppm.

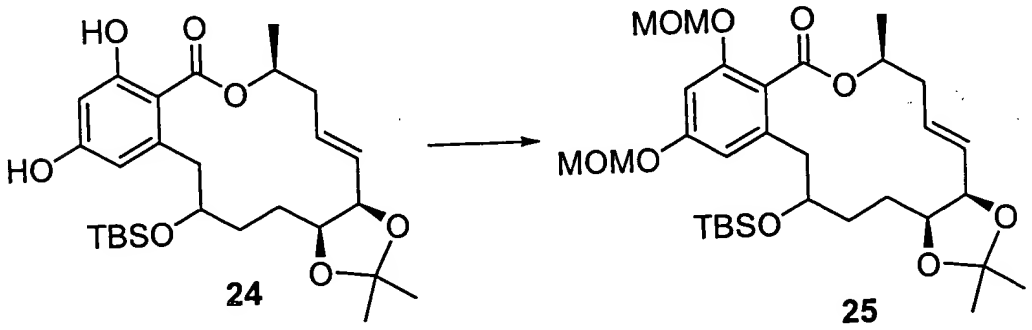


Resorcyclic macrolide 24:

Macrolide **7A** (26 mg, 0.065 mmol) was transferred to a vial and 0.2 mL diene **8** was added. The vial was sealed and heated to 140 0 °C for 36 h. The crude mixture was purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000 μM) using Hexanes/EtOAc (2/1) as the eluant to afford **24A** as a colorless oil (23 mg, 74%). $[\alpha]_D^{25}$ -99.1 (*c* 0.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ -0.15, (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.36 (s, 3 H), 1.38 (s, *J* = 6.1 Hz, 1 H), 1.50 (s, 3 H), 1.25-1.39 (m, 4 H), 1.71-1.76 (m, 1 H), 2.54-2.57 (m, 2 H), 2.60-2.64 (m, 1 H), 3.63-3.68 (m, 2 H), 4.08-4.11 (m, 1 H), 4.48 (m, 1 H), 5.22-5.26 (m, 1 H), 5.54 (bs, 1 H), 5.70-5.75 (m, 2 H), 6.27 (d, *J* = 2.6 Hz, 1 H), 6.28 (d, *J* = 2.6 Hz, 1 H), 11.3 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, -4.1, 0.4, 14.6, 18.4, 21.3, 21.5, 24.1, 25.9, 26.3, 28.6, 32.4, 40.1, 42.4, 70.0, 73.5, 73.7, 77.7,

79.7, 101.9, 106.6, 108.7, 111.6, 130.5, 131.6, 145.7, 160.4, 165.0, 172.1. HRMS (FAB) calcd for $C_{27}H_{42}O_7SiH^+$ $[M+H]^+$: 507.2778, found: 507.2777, $\Delta = 0.2$ ppm.

24B was prepared by same procedure from **7B**. **24B**: (81 mg, 84%). $[\alpha]_D^{25}$ -124.2 (*c* 0.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.00, (s, 3 H), 0.14 (s, 3 H), 0.99 (s, 9 H), 1.50 (s, 3 H), 1.58 (d, $J = 6.1$ Hz, 1 H), 1.40-1.67 (m, 2 H), 1.64 (s, 3 H), 1.87-1.92 (m, 2 H), 2.64-2.72 (m, 2 H), 3.09 (dd, $J = 3.8$ Hz, 2.5 Hz, 1 H), 3.45 (dd, $J = 13.8$, 7.8 Hz, 1 H), 4.02-4.04 (m, 1 H), 4.20-4.22 (m, 1 H), 4.70-4.74 (m, 1 H), 5.50-5.52 (m, 1 H), 5.76 (dd, $J = 15.5$, 8.1 Hz, 1 H), 5.93-5.95 (m, 2 H), 6.42 (m, 1 H), 6.48 (m, 1 H), 11.62 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3, -4.0, 14.5, 18.3, 18.4, 20.5, 21.5, 25.8, 26.2, 28.3, 28.4, 28.5, 33.1, 61.1, 72.7, 73.5, 79.1, 102.1, 107.1, 108.5, 112.7, 130.1, 130.5, 144.2, 160.7, 164.9, 171.7. LRMS (ESI) calcd for $C_{27}H_{42}O_7SiNa^+$ $[M+Na]^+$: 529.2, found: 529.1. LRMS (ESI) calcd for $C_{27}H_{42}O_7SiCl^-$ $[M+Cl]^-$: 541.3, found: 541.2.



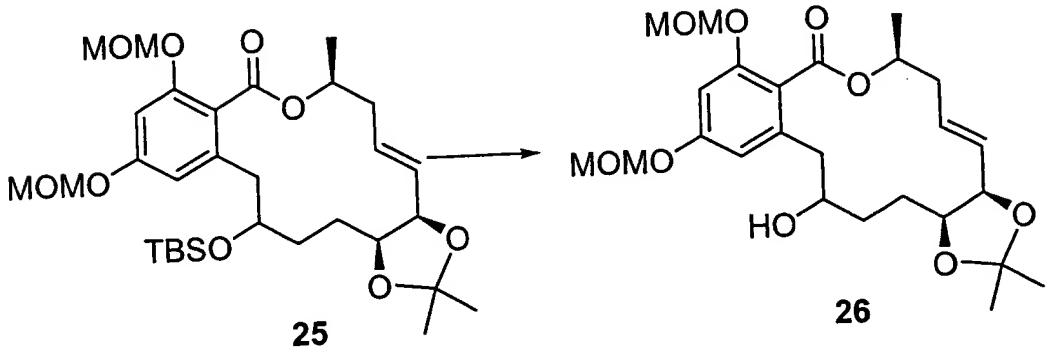
MOM ether 25:

To a solution of **24A** (23 mg, 0.045 mmol) in CH_2Cl_2 (0.5 mL) was added diethylpropylethylamine (0.08 mL, 0.450 mmol) and MOMCl (0.018 mL, 0.227 mmol). The reaction mixture was stirred for 10 h before quenched with saturated aqueous NH_4Cl

solution, extracted with EtOAC (100 mL X 3). The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000 μM) using Hexanes/EtOAc (2/1) as the eluant to afford **25A** as a colorless oil (21 mg, 78%). $[\alpha]_D^{25}$ -2.86 (*c* 0.07, $CHCl_3$).). ^1H NMR (400 MHz, $CDCl_3$) δ 0.00, (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 1.39 (s, 3 H), 1.39 (d, 3 H), 1.48 (s, 3 H), 1.42-1.48 (m, 1 H), 1.60-1.64 (m, 2 H), 1.72-1.77 (m, 1 H), 2.41-2.45 (m, 2 H), 2.66 (dd, *J* = 5.6, 4.6 Hz, 1 H), 2.89 (dd, *J* = 4.5, 1.6 Hz, 1 H), 3.47 (s, 3 H), 3.48 (s, 3 H), 3.97-3.98 (m, 1 H), 4.09-4.15 (m, 1 H), 4.73 (dd, *J* = 9.0, 6.0 Hz, 1 H), 5.13-5.19 (m, 4 H), 5.30-5.36 (m, 1 H), 5.57 (dd, *J* = 15.4, 9.1 Hz, 1 H), 5.70-5.77 (m, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 6.86 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3, -4.2, 0.5, 18.4, 21.6, 24.0, 25.9, 26.3, 28.7, 30.1, 32.3, 40.1, 40.4, 56.5, 56.6, 71.4, 71.6, 80.3, 94.7, 94.9, 101.8, 108.5, 111.4, 119.8, 130.2, 132.4, 139.4, 155.3, 158.6, 168.4.

25B was prepared by same procedure from **24B**. **25B**: (58 mg, 83%). $[\alpha]_D^{25}$ -16.2 (*c* 0.29, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ -0.17 (s, 3 H), -0.06 (s, 3 H), 0.81 (s, 9 H), 1.26 (s, 3 H), 1.33 (d, *J* = 6.1 Hz, 1 H), 1.38 (s, 3 H), 1.17-1.52 (m, 4 H), 2.30-2.36 (m, 2 H), 2.61 (dd, *J* = 14.2, 6.0 Hz, 1 H), 2.71 (dd, *J* = 14.2, 6.9 Hz, 1 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.80-3.83 (m, 1 H), 4.10-4.14 (m, 1 H), 4.41 (dd, *J* = 8.9, 6.1 Hz, 1 H), 5.04-5.09 (m, 4 H), 5.20-5.23 (m, 1 H), 5.43 (dd, *J* = 15.3, 9.1 Hz, 1 H), 5.60-5.67 (m, 1 H), 6.46 (s, 1 H), 6.60 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.2, -3.8, 18.4, 21.3, 25.8, 26.2, 26.25, 26.3, 28.6, 33.0, 39.8, 40.0, 42.0, 56.5, 56.6, 71.7, 74.5, 78.6, 79.9, 94.7, 94.9, 101.5,

108.3, 111.2, 119.8, 131.0, 131.4, 139.2, 155.8, 158.9, 168.5. HRMS (FAB) calcd for $C_{31}H_{50}O_9SiH^+$ $[M+H]^+$: 595.3302, found: 595.3304, Δ = -0.3 ppm.



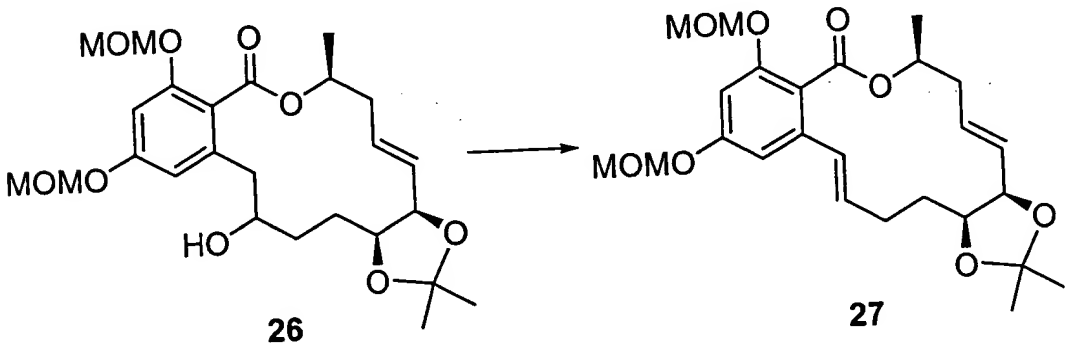
25 26

Alcohol 26:

To a solution of **25A** (21 mg, 0.035 mmol) in THF (1.4 mL) was added pyridine (0.6 mL) and HF-pyridine (30%, 0.3 mL). The reaction mixture was stirred for 10 h before quenched with MeOTf (2 mL) and stirred for 1 h. The solvent was removed under reduced pressure vacuum. The residue was purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000 μM) using Hexanes/EtOAc (1/1) as the eluant to afford **26A** as a colorless oil (12 mg, 78%). $[\alpha]_D^{25}$ -105.2 (*c* 0.06, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 3 H), 0.05 (s, 3 H), 1.35 (s, 3 H), 1.38 (d, *J* = 6.2 Hz, 3 H), 1.46 (s, 3 H), 1.61-1.81 (m, 4 H), 2.40-2.46 (m, 2 H), 2.70 (dd, *J* = 14.1, 6.1 Hz, 1 H), 2.81 (dd, *J* = 14.1, 4.7 Hz, 1 H), 3.46 (s, 6 H), 3.89 (b, 1 H), 4.10-4.14 (m, 1 H), 4.56 (dd, *J* = 9.1, 6.1 Hz, 1 H), 5.13-5.17 (m, 4 H), 5.32-5.37 (m, 1 H), 5.59 (dd, *J* = 15.4, 9.2 Hz, 1 H), 5.70-5.75 (m, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 6.70 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.1, 25.7, 28.6, 30.1, 32.3, 40.0, 41.6, 56.6, 56.7, 70.5, 72.0, 80.1, 94.7,

94.9, 101.9, 108.2, 111.0, 119.7, 130.6, 132.7, 138.3, 155.8, 159.1, 168.4. HRMS (FAB) calcd for $C_{25}H_{36}O_9H^+$ $[M+H]^+$: 482.2438, found: 482.2437, $\Delta = 0.1$ ppm.

26B was prepared by same procedure from **25B**. **26B**: (20 mg, 87%). $[\alpha]_D^{25}$ -32.0 (*c* 0.10, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (m, 2 H), 1.35 (s, 3 H), 1.37 (d, $J = 6.2$ Hz, 1 H), 1.42 (s, 3 H), 1.55-1.69 (m, 2 H), 1.98-2.06 (m, 1 H), 2.42-2.48 (m, 3 H), 2.78 (dd, $J = 13.8$, 2.4 Hz, 1 H), 3.41-3.50 (m, 6 H), 3.62-3.67 (m, 1 H), 4.19-4.25 (m, 1 H), 4.49 (dd, $J = 9.4$, 6.0 Hz, 1 H), 5.11-5.18 (m, 4 H), 5.36-5.42 (m, 1 H), 5.56 (dd, $J = 15.4$, 9.5 Hz, 1 H), 5.65-5.72 (m, 1 H), 6.57 (d, $J = 2.0$ Hz, 1 H), 6.66 (d, $J = 2.0$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.8, 26.8, 28.6, 32.0, 39.8, 42.6, 56.5, 56.7, 72.3, 74.8, 80.3, 94.7, 94.9, 101.8, 108.6, 110.7, 108.6, 110.7, 119.5, 129.9, 132.8, 138.7, 155.9, 159.0, 168.7. HRMS (FAB) calcd for $C_{25}H_{36}O_9H^+$ $[M+H]^+$: 482.2438, found: 482.2437, $\Delta = 0.1$ ppm.

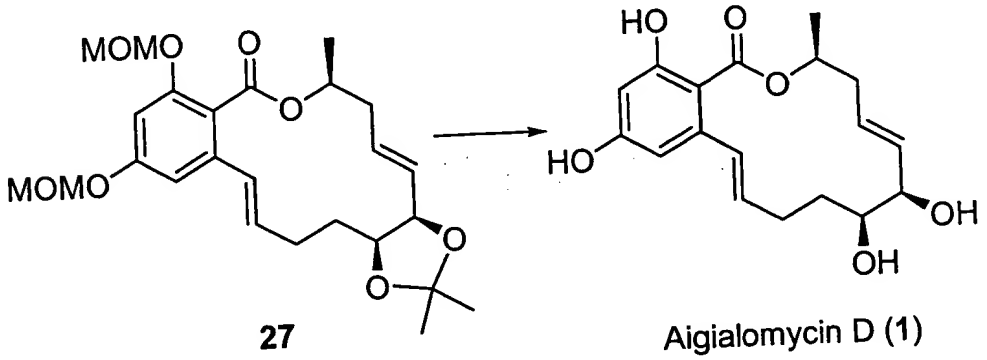


Diene 27:

A solution of Martin's sulfurane dehydration agent (140 mg, 0.208) was added into a vial containing **26B** (20 mg, 0.042) at 0 °C. The reaction mixture was warmed up to r.t. over 2 h and the crude was purified on preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000

μM) using Hexanes/EtOAc (1/1) as the eluant to afford **27** as a colorless oil (16 mg, 84%). $[\alpha]_D^{25}$ -123.8 (*c* 0.08, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.36 (d, *J* = 6.0 Hz, 3 H), 1.46 (s, 3 H), 1.49-1.55 (m, 1 H), 1.80-1.85 (m, 1 H), 2.07-2.11 (m, 1 H), 2.29-2.32 (m, 1 H), 2.45-2.55 (m, 2 H), 3.41-3.50 (m, 6 H), 4.16-4.21 (m, 1 H), 4.56 (dd, *J* = 9.5, 5.4 Hz, 1 H, 1 H), 5.10-5.20 (m, 4 H), 5.32-5.36 (m, 1 H), 5.59 (dd, *J* =15.5, 9.6 Hz, 1 H), 5.70-5.77 (m, 1 H), 5.15 (m, 1 H), 6.24 (d, *J* = 15.4 Hz, 1 H), 6.80 (d, J = 1.8 HZ, 1 H), 6.68 (d, J = 1.8 HZ, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 25.8, 28.6, 28.7, 29.0, 39.5, 71.6, 80.1, 84.3, 94.6, 102.6, 104.8, 108.3, 117.9, 124.8, 128.4, 129.3, 131.9, 132.3, 136.8, 155.1, 158.9, 167.3. HRMS (FAB) calcd for $C_{25}H_{34}O_8H^+$ $[M+H]^+$: 463.2332, found: 463.2333, Δ = -0.2 ppm.

27 could also be obtained from **26A** using same procedure (90%).



27 Aigialomycin D (1)

Aigialomycin D (1):

To a solution of **27** (16 mg, 0.035) in MeOH (1.5 mL) was added HCl (1 *N*, 1.5 mL) and stirred for 2 d. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced vacuum. The crude was purified on

preparative TLC (Whatman® Pk6F Silica Gel 60 Å 1000 μM) using MeOH/CH_2Cl_2 (5%) as the eluant to afford **1** as a white solid (8 mg, 69%). Mp: 84.2-86.9 °C. $[\alpha]_D^{25}$ -18.0 (*c* 0.03, MeOH). IR (neat) 3346, 1643, 1607, 1311, 1261, 1166, 1017, 968. ^{1}H NMR (500 MHz, acetone-d_6) δ 1.39 (d, J = 6.4 Hz, 3 H), 1.58-1.61 (m, 1 H), 2.14 (m, 1 H), 2.32-2.36 (m, 2 H), 2.43-2.46 (m, 1 H), 2.57 (ddd, J = 14.5, 7.3, 3.1 Hz, 1 H), 3.56 (br, 1 H), 3.64 (m, 1 H), 3.76 (br, 1 H), 4.35 (brd, J = 4.1 Hz, 1 H), 5.41-5.47 (m, 1 H), 5.69 (dd, J = 15.6, 5.1 Hz, 1 H), 5.87 (dddd, J = 15.6, 7.4, 7.4, 1.4 Hz, 1 H), 6.10 (ddd, J = 15.9, 5.5, 5.7 Hz, 1 H), 6.28 (d, J = 2.3 Hz, 1 H), 6.53 (d, J = 2.3 Hz, 1 H), 7.16 (d, J = 15.9 Hz, 1 H), 9.10 (bs, 1 H), 11.7 (s, 1 H). ^{13}C NMR (125 MHz, acetone-d_6) δ 19.2, 28.1, 28.8, 38.1, 73.1, 73.4, 76.7, 102.6, 104.6, 107.9, 125.6, 130.8, 133.8, 135.9, 144.5, 163.2, 166.0, 172.3. LRMS (ESI) calcd for $C_{18}H_{22}O_6Na^+$ $[Na+H]^+$: 357.1, found: 357.3. LRMS (ESI) calcd for $C_{18}H_{21}O_6^-$ $[M-H]^-$: 333.1, found: 333.1. LRMS (ESI) calcd for $C_{18}H_{22}O_6Cl^-$ $[M+Cl]^-$: 369.1, found: 369.0. HRMS (TOF) calcd for $C_{18}H_{22}O_6Na^+$ $[M+Na]^+$: 357.1314, found: 357.1325, Δ = 3.1 ppm. All the physical data are consistent with the reported value.[2]

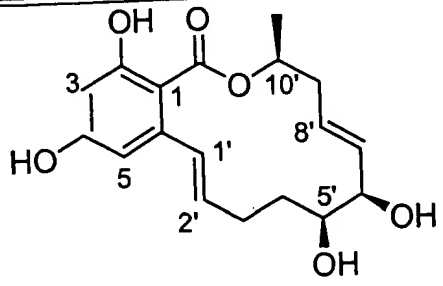
Reference:

1. Barbat, J.; Gelas, J.; Horton, D. *Carbohydrate Res.* **1983**, *116*, 312-316.

2. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561-1566.

Table 1. ^{1}H NMR Data of Aigialomycin D

position	Isolated Aigialomycin D by Isaka[2]	Synthetic Aigailomycin D
3	6.27 (d, 2.4)	6.28 (d, 2.3)
5	6.52 (d, 2.4)	6.53 (d, 2.3)
1'	7.14 (d, 15.9)	7.16 (d, 15.9)
2'	6.09 (ddd, 15.9, 5.6, 5.4)	6.10 (ddd, 15.9, 5.7, 5.5)
3'	2.31-2.34 (m)	2.32-2.36 (m)
	2.31-2.34 (m)	2.32-2.36 (m)
4'	2.14 (m)	2.14 (m)
	1.58 (m)	1.58-1.61 (m)
5'	3.62 (m)	3.64 (m)
6'	4.35 (brd, 4.3)	4.35 (brd, 4.1)
7'	5.68 (dd, 15.7, 5.0)	5.69 (dd, 15.6, 5.1)
8'	5.87 (dddd, 15.7, 7.3, 7.3, 1.2)	5.87 (dddd, 15.6, 7.4, 7.4, 1.4)
9'	2.55 (ddd, 14.6, 7.5, 3.2)	2.55 (ddd, 14.5, 7.3, 3.1)
	2.42 (m)	2.43-2.46 (m)
10'	5.42 (m)	5.41-5.47 (m)
10'-CH_3	1.38 (d, 6.4)	1.39 (d, 6.4)
2-O*H*	11.65 (s)	11.7 (s)
4-O*H*	9.5 (br)	9.1 (br)
5'-O*H*	not detected	3.56 (br)
6'-O*H*	not detected	3.76 (br)



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